A CLINICAL COMPARISON BETWEEN BUPIVACAINE (PLAIN) AND BUPIVACAINE-MIDAZOLAM IN BRACHIAL PLEXUS BLOCK VIA SUPRACLAVICULAR APPROACH

A STUDY OF 100 CASES

Dissertation submitted for the degree of

DOCTOR OF MEDICINE

Branch – X (ANAESTHESIOLOGY)

APRIL – 2015

TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI,

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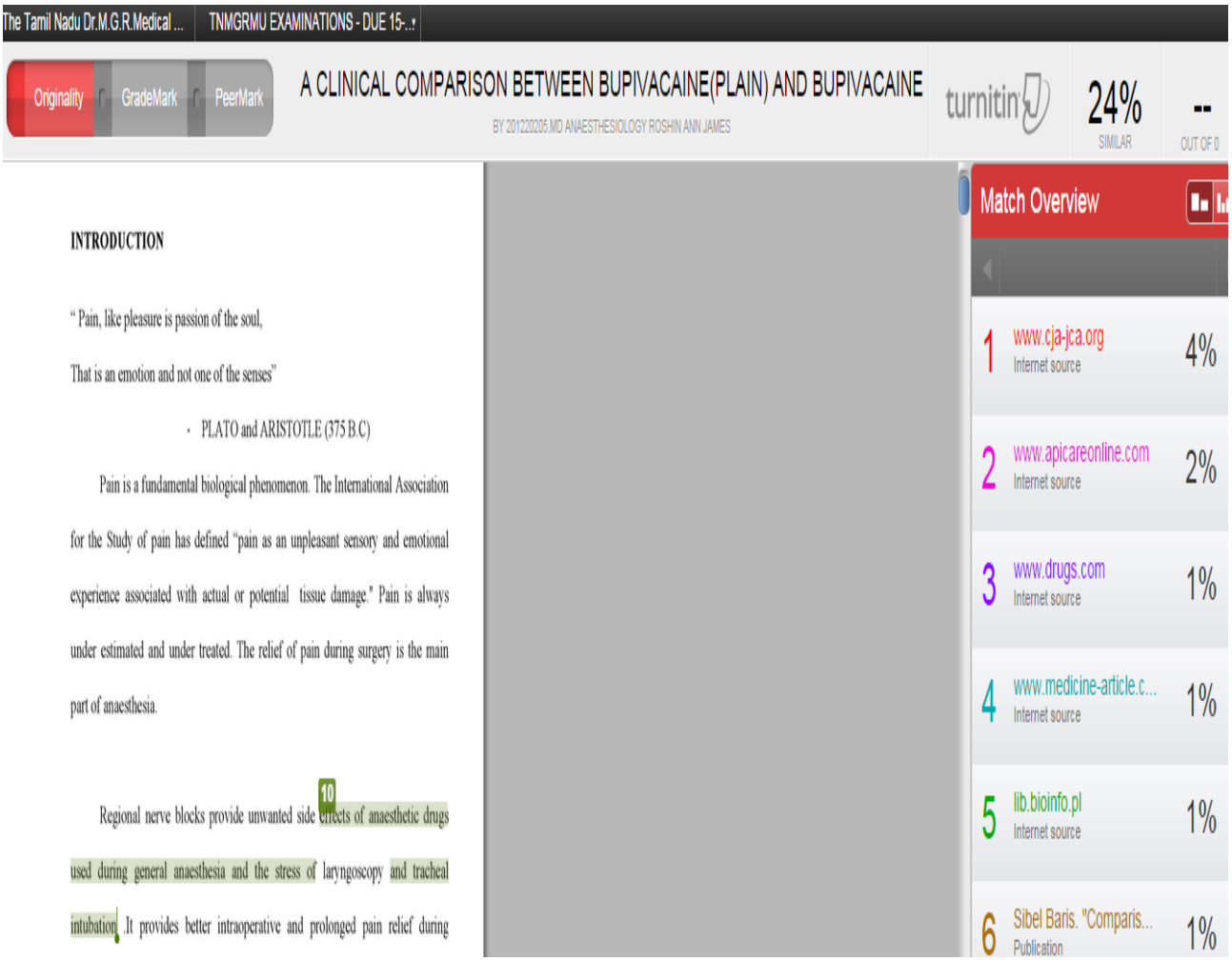
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INTRODUCTION
" Pain, like pleasure is passion of the soul,
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- PLATO and ARISTOTLE (375 B.C)
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Regional nerve blocks provide unwanted side effects of anaesthetic drugs used during general anaesthesia and the stress of laryngoscopy and tracheal intubation .It provides better intraoperative and prolonged pain relief during
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LIST OF ABBREVIATIONS USED

μg	-	microgram
ASA	-	American Society of Anaesthesiologists (classification)
BT	-	Bleeding time
BZD	-	Benzodiazepine
cm	-	centimetre
CT	-	Clotting Time
DBP	-	Diastolic Blood Pressure
dl	-	Decilitre
ECG	-	Electro Cardio Gram
GABA	-	Gamma Amino Butyric Acid
gm	-	gram
HBsAg	-	Hepatitis B Antigen
HIV	-	Human Immunodeficiency Virus
HS	-	Highly significant
IM	-	Intramuscular
IV	-	Intravenous
Kg	-	Kilogram
LA	-	Local Anaesthetic
MAP	-	Mean Arterial Pressure
Min	-	Minutes
ml	-	Millilitre
mm of Hg	-	Millimetre of mercury
NS	-	Not significant
pKa	-	Dissociation constant
RA	-	Rescue analgesics
S	-	Significant
S.D.	-	Standard Deviation
SBP	-	Systolic Blood Pressure

ABSTRACT

Background and objectives : Adjuvants to local anaesthetics for brachial plexus block enhances the quality and duration of analgesia. Midazolam , a water-soluble benzodiazepine, is known to produce antinociception and enhance the effect of local anaesthetics when given epidurally or intrathecally. The purpose of this study was to assess the effect of Midazolam added to brachial plexus block by supraclavicular approach.

Methods : A prospective, randomized, single blinded study was conducted on 100 ASA I or II adult patients undergoing upper limb surgeries under supraclavicular brachial plexus block. Patients were randomly divided into two groups. Patients in Group B (n = 50) were administered 30mL of 0.375% Bupivacaine and Group BM (n = 50) were given 30mL of 0.375% Bupivacaine with Midazolam 2.5 mg. The onset time and duration of sensory and motor blockade were recorded. Hemodynamic variables (i.e., heart rate, noninvasive blood pressure, oxygen saturation), sedation scores and rescue analgesic requirements were recorded for 24 hr postoperatively.

Results : The onset of sensory and motor block was significantly faster in Group BM compared to Group B ($P < 0.05$). Rescue analgesic requirements were significantly less in Group BM compared to Group B ($P < 0.05$). Haemodynamics and sedation scores did not differ between the two groups in the post-operative period.

Conclusion : Midazolam (2.5mg) in combination with 30mL of Bupivacaine (0.375%) hastened onset of sensory and motor block, and prolonged postoperative analgesia when used in brachial plexus block, without producing any adverse effects.

Keywords : *Supraclavicular brachial plexus block; Midazolam; Bupivacaine.*

TABLE OF CONTENTS

LIST OF TABLES

LIST OF GRAPHS

LIST OF FIGURES

Introduction

INTRODUCTION

“ Pain, like pleasure is passion of the soul,

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- PLATO and ARISTOTLE (375 B.C)

Pain is a fundamental biological phenomenon. The International Association for the Study of pain has defined “pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage." Pain is always under estimated and under treated. The relief of pain during surgery is the main part of anaesthesia.

Regional nerve blocks provide unwanted side effects of anaesthetic drugs used during general anaesthesia and the stress of laryngoscopy and tracheal intubation .It provides better intraoperative and prolonged pain relief during postoperative period. Minimising the stress response and minimising anaesthetic drug requirements are beneficial to the patients with various cardiorespiratory comorbidities.

Brachial plexus blocks provide a wonderful alternative to general anaesthesia for upper limb surgeries. They achieve near-ideal operative conditions by providing complete and prolonged pain relief, muscle relaxation, maintaining stable intra-operative hemodynamics and adequate sympathetic block. The sympathetic block decreases postoperative pain, vasospasm and edema.[1]

Of various local anaesthetics, Bupivacaine is used most frequently, as it has a long duration of action varying from 3 to 8 hours. However there are many limiting factors like delayed onset, patchy or incomplete analgesia, sometimes of short duration etc. Various drugs like Dexmedetomidine, Opioids[2],Hyaluronidase[3], Clonidine etc[4].have been added to local anaesthetics in order to modify the block in terms of quicker onset, good quality, prolonged duration and post operative analgesia. But these presented with adverse systemic effects or doubtful efficacy.[4]

Midazolam, a water-soluble benzodiazepine is known to produce antinociception and enhance the effect of local anaesthetic when given epidurally or intrathecally[5]. Midazolam produces this effect by its action on gamma aminobutyric acid-A (GABA-A) receptors. GABA receptors have also been found in peripheral nerves[5].

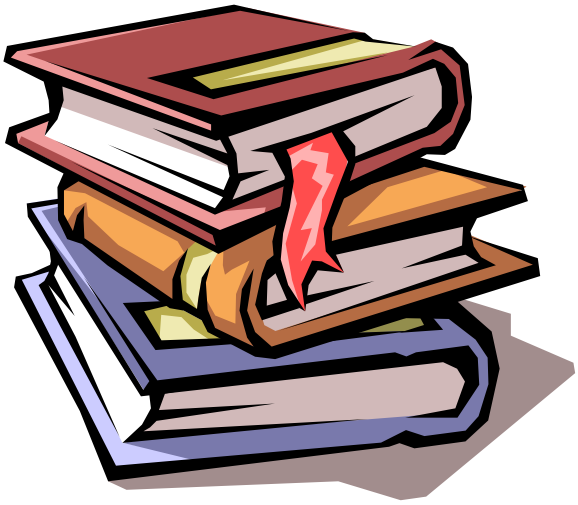
So the present study is being undertaken in a randomized single blinded manner to evaluate the onset time and analgesic efficacy of Midazolam(preservative free)- Bupivacaine combination compared to plain Bupivacaine(0.375%) for brachial plexus block by supraclavicular approach.

Aim of the study

AIM OF THE STUDY

The present study was undertaken to compare the efficacy of adding midazolam (2.5mg) to bupivacaine (0.375%) in supraclavicular technique of brachial plexus block for upper limb surgeries with respect to

1) Onset time and duration of sensory and motor blockade.
2) Hemodynamic changes
3) Sedation score intra and post-operatively
4) Number of rescue analgesics required in the 24 hour post-operative period.



Brachial Plexus Block

HISTORY

1. 1858 – theory of pain was a separate and distinct sense was definitely formulated by Mortiz S.Schiff
2. 1884 – William Halsted and Alfred Hall – idea of injecting cocaine into nerve trunk
3. 1911 – G. Hirschel performed first percutaneous axillary brachial plexus block
4. 1911 – D. Kulenkampff performed supraclavicular brachial plexus block
5. 1943 - Lidocaine was synthesized by Lofgreen and Lundquvisit
6. 1956 – Bupivacaine synthesized by Ekenstam
7. 1963 – Bupivacaine introduced clinical practice by Telivuo
8. Melzock and Walts (1965) propounded the Gate Control Theory of pain.

ANATOMY OF BRACHIAL PLEXUS [6,7]

Knowledge of formation of brachial plexus and its ultimate cutaneous and muscular distribution is absolutely essential to the intelligent and effective use of brachial plexus anaesthesia for upper limb surgeries. Close familiarity with the vascular, muscular and fascial relationships of the plexus is equally essential to the mastery of various techniques , for it is these perineural structures which serve as the landmark by which needle may accurately locate the plexus percutaneously.

In its course from intervertebral foramina to the upper arm, the fibres are composed consecutively of roots, trunks, divisions, cords and terminal nerves.

FORMATION OF BRACHIAL PLEXUS :

Brachial plexus is formed by the union of ventral rami of lower four cervical nerves (C5, 6,7,8) and first thoracic nerve (T1) with frequent contributions from C4 or T2.When contribution from C4 is large and from T2 is lacking, the plexus appears to have a more cephaloid position and is termed "Prefixed". When contribution from T2 is large and from C4 is lacking, the plexus appears to have a caudal position and is termed "postfixed". Usually prefixed or postfixed positions are associated with the presence either of a cervical rib or of an anomalous first rib.[6]

ROOTS :

Represent the anterior primary divisions of lower four cervical and first thoracic nerves. They emerge from the intervertebral foramina and fuse above the first rib to form the trunks.

TRUNKS :

The roots combine above the first rib to form the three trunks of the plexus. C5 and C6 unite at the lateral border of the scalenus medius and form the "Upper trunk".C8 and T1 unite behind the scalenus anterior to form "lower trunk" and C7 continues as a sole contributor to the "middle trunk".

DIVISIONS :

As the trunks pass over the first rib and under the clavicle, each one of them divides into anterior and posterior divisions.

CORDS :

The fibres, as they emerge from under the clavicle, recombine to form three cords. The "lateral cord" is formed by anterior divisions of upper and middle trunks, lateral to the axillary artery. The anterior division of lower trunk descend medial to the axillary artery forming the "medial cord". The posterior divisions of all three trunks unite to form the

"posterior cord", at first above and then behind the axillary artery. The medial and lateral cords give rise to nerves that supply the flexor surface of upper extremity, while nerves arising from posterior cord supply extensors[7]

MAJOR TERMINAL NERVES :

Each of these cords gives off a branch that contributes to or become one of the major nerves to the upper extremity and then terminates as a major nerve. The lateral and median cords give off lateral and medial heads of the medial nerve and continue as major terminal nerves, the lateral cord terminating as musculocutaneous nerve and medial cord as ulnar nerve. Posterior cord gives off, axillary nerve as its major branch and then continues as the radial nerve.

DISTRIBUTION OF BRACHIAL PLEXUS :

These are divided into those that arise above the clavicle – the supraclavicular branches and those that arise below it, the infraclavicular branches.

Supraclavicular branches :

From roots :

1. Nerves to scaleni and longus colli – $C_{5,6,7,8}$
2. Branch to phrenic nerve – C_5
3. Dorsal scapular nerve – C_5
4. Long thoracic nerve – $C_{5,6,(7)}$

From trunks :

1. Nerve to subclavius – $C_{5,6}$
2. suprascapular nerve – $C_{5,6,}$

Infraclavicular branches : They branch from cords but their fibres may be tracked back to spinal nerves.

Lateral cord :

1. Lateral pectoral nerve – $C_{5,6,7}$
2. Musculocutaneous nerve – $C_{5,6,7}$
3. Lateral root of median nerve – $C_{5,6,7}$

Medial cord :

1. Medial pectoral nerve – C_8, T_1
2. Medial cutaneous nerve of forearm – C_8, T_1
3. Ulnar nerve – C_8, T_1
4. Medial root of median nerve – C_8, T_1
5. Medial cutaneous nerve of arm – C_8, T_1

Posterior cord :

1. Upper subscapular nerve – $C_{5, 6}$
2. Thoracodorsal nerve – $C_{6, 7, 8}$
3. Lower subscapular nerve – $C_{5, 6}$
4. Axillary nerve – $C_{5, 6}$
5. Radial nerve - – $C_{5, 6, 7, 8, T1}$

SYMPATHETIC CONTRIBUTION TO BRACHIAL PLEXUS :

The segmental preganglionic sympathetic contributions are variable, but generally extend more caudal. The highest contribution is usually T2 with T1 contributing only rarely, while lowest may be as far as T8, T9 or even T10. The post ganglionic contributions are from grey rami communicants from the sympathetic chain.

RELATIONS OF BRACHIAL PLEXUS :[8]

In its passage from the cervical transverse processes to the first rib, the plexus is "sandwiched" between the anterior and middle scalene muscles and invested in the fascia of those two muscles. The 'interfascial compartment', along with subclavian artery which crosses the first rib immediately in front of the trunks. Artery is close to the scalenus anterior and the plexus close to the scalenus medius. Subclavian vein is separated from the artery by the

scalenus anterior. The fascia covering the muscles is derived from the perivertebral fascia, which splits to invest these muscles and rejoins again at their lateral margins to form an enclosed space, the interscalene space.

As the plexus crosses the first rib, the three trunks are 'stacked' one on top of the other vertically. Not infrequently, the inferior trunk gets trapped behind and even beneath the subclavian artery above the rib, during embryologic development. This may be reason why local anaesthetics injected via the interscalene technique sometimes fail to provide anaesthesia in the distribution of the ulnar nerve, which may be buried deep within inferior trunk behind or beneath the subclavian artery.

After crossing the first rib, they split to form 2 divisions and the cords and subclavian artery becomes the axillary artery. Above the clavicle, the axillary artery lies central to the three cords, in the axilla the lateral and posterior cords are lateral to the first part of the axillary artery, the medial cord being behind it. Around the second part of the artery, they are related according to their names. In the lower axilla, cords divide into nerves for the upper limb. In passing over the first rib under the clavicle, the subclavian vein also becomes the axillary vein and its relationship with the neurovascular bundle changes. Above the first rib the subclavian vein does not lie within the neurovascular bundle, it is separated by the insertion of

scalenus anterior.

As it passes over the first rib, becoming the axillary vein it joins the neurovascular bundle so that parts of the plexus are sandwiched between artery and vein. As all the three enter the axilla, they invaginate the perivertebral fascia at the lateral margins of the anterior and medial scalene muscles, carrying this fascial investment of the neurovascular bundle into the axilla as the axillary fascia, an extension of the perivertebral or scalene fascia forming the axillary perivascular space, a tubular extension of the interscalene space.

In its course through the axilla and upper arm the fascia of the surrounding muscles contribute to the axillary sheath, making it thick and tough, providing the 'fascial click' to the anaesthetic while entering the sheath. It is important to note that major terminal nerves leave the sheath high in the axilla undercover of perctoralis minor muscle.

The musculocutaneous nerve enters the substance of coracobrachialis and continues down within this muscle. The axillary nerve also leaves the sheath immediately after arising from the posterior cord. The intercostobrachial nerve travels parallel to but outside the axillary sheath and medial cutaneous nerve of the arm runs similarly but occasionally it may remain within the sheath.

THE BRACHIAL PLEXUS SHEATH

Volume of the sheath : 42ml.

Shape of the sheath : Cylindrical to conical – Wide proximally and narrow distally.

Length : 8-10cms long.

The connective tissue of the prevertebral fascia and the anterior and middle scalenes envelops the brachial plexus as well as the subclavian and axillary artery in a neurovascular "sheath".The tissue is densely organized as it leaves the deep cervical fascia proximally but becomes more loosely arranged distally. The sheath blends with the fascia of the biceps and brachialis muscle distally.

Anatomic dissection, histologic examination and CT scanning after injection of radio contrast into the sheath demonstrate the existence of connective tissue septae which extend inward from the fascia surrounding the sheath. The thin velamentous connective tissue septae frequently adhere to the nerves and vessels leaving no free space between the layers and compartmentalizing the components of the sheath.

Anaesthetic Implications :

Because of these connective tissue septae, anaesthesia might be complete and rapid in onset in some nerves, but delayed and incomplete or completely absent in others. The incidence of partial block is an exception rather than the rule, so septa apparently are of little clinical significance as the local anaesthetic can percolate through them.

TECHNIQUE OF BRACHIAL PLEXUS BLOCK[9]

Surgical anaesthesia of the upper extremity and shoulder can be obtained following neural blockade of the brachial plexus at several sites. The various approaches that can be used for this blockade are as follows

1.Interscalene approach

2. Supraclavicular approach

a. Classic approach

b. Plumb –bob technique

c. Subclavian perivascular technique

3. Axillary approach

4. Infraclavicular approach

Supraclavicular approach [10]

a. Classic approach

Patient Position: Supine, with the head turned to the opposite side and the arm adducted and the shoulder dropped.

Indications: Anesthesia and immediate postoperative analgesia for surgery above the elbow, or at the elbow, forearm, wrist, or hand.

Needle Size: 22-gauge , 5-cm insulated needle.

Volume: 30 to 40 mL.

Anatomic Landmarks: The lateral border of the clavicular head of the sternocleidomastoid at its insertion into the clavicle, the subclavian artery, and the anterior and middle scalene muscles.

Approach and Technique: First, the lateral border of the sternocleidomastoid, particularly at the level of its insertion into the clavicle, is marked. Next, the interscalene groove is identified and marked. The palpating finger is placed parallel and immediately superior to the clavicle at the level of the subclavian artery and the interscalene groove. The insulated needle, connected to a nerve

stimulator (1.0 mA, 2 Hz, 0.1 ms) is inserted posterior to the palpating finger (**Fig. 4**). The needle is directed caudad and lateral, so as to cross the clavicle almost perpendicularly. A muscle response involving the arm and fingers either in flexion or extension is elicited within 2 to 3 cm. The position of the needle is adjusted to maintain the same motor response with a current of 0.5 to 0.7 mA. After negative aspiration for blood, the local anesthetic is slowly injected with repeated aspiration for blood every 5 mL to be distributed around the brachial plexus

B) Plumb bob approach[10]

Patient Position: Supine, with the head turned to the opposite side and the arm adducted and the shoulder dropped.

Approach and Technique Patient's head is slightly off the back table so that lateral border of sternocleidomastoid is marked as it inserts to the clavicle.From that point,a mental plane is visualised that runs parasagittaly through that site. "Plumb blob" was chosen,since if one suspends a "plumb-blob"over the entry site,needle insertion through the point will result in contact with brachial plexus mostly.Brachial plexus lies posterior and cephalad to subclavian artery at the level of first rib.Once the skin mark has been placed,immediately superior to the clavicle at the lateral border of

sternocleidomastoid ,needle is inserted in parasagittal plane at 90^0 angle to the table top.Once paraesthesia has been elicited, after negative aspiration for blood, the local anesthetic is slowly injected with repeated aspiration for blood every 5 mL to be distributed around the brachial plexus.

LOCAL ANESTHETIC MECHANISMS IN NERVE BLOCKADE[11]

Impulse blockade by local anesthetics may be summarized by the following chronolog:

• Solutions of local anesthetic are deposited near the nerve. Removal of free drug molecules away from this locus is a function of tissue binding, removal by the circulation, and local hydrolysis of amino-ester anaesthetics. The net result is penetration of the nerve sheath by the remaining free drug molecules.

• Local anesthetic molecules then permeate the nerve‘s axon membranes and reside there and in the axoplasm. The speed and extent of these processes depend on a particular drug‘s pκa and on the lipophilicity of its base and cation species.

• Binding of local anesthetic to sites on voltage-gated Na+ channels prevents opening of the channels by inhibiting the conformational changes that underlie channel activation. Local anesthetics bind in the channel’s pore and also occlude the path of Na+ ions.

• During onset or recovery from local anesthesia, impulse blockade is incomplete and partially blocked fibres are further inhibited by repetitive stimulation, which produces an additional use-dependent blinding to Na+ channels.

• One local anesthetic binding site on the Na+ channel may be sufficient to account for the drug's resting (tonic) and use-dependent (phasic) actions Access to this site may potentially involve multiple pathways, but for clinical local anesthetics, the primary route is the hydrophobic approach from within the axon membrane.

• The clinically observed rates of onset and recovery from blockade are governed by the relatively slow diffusion of local anesthetic molecule into and out of the whole nerve, not by their much faster binding and dissociation from ion channels. A clinically effective block that may last for hours can be accomplished with local anesthetic drugs that dissociate from Na+ channels in a few seconds[11].

COMPLICATIONS[12]

Vascular puncture

Internal jugular vein may be punctured at skin wheal infiltration. Simple digital compression is required before continuing, the likelihood of arterial puncture implies not to pinpoint behind and too medial from midclavicle. Best is to withdraw and redirect the needle when perceiving artery pulsation at the needle tip.

Pleural puncture

The most significant complication of supraclavicular approach for blocking brachial plexus is development of pneumothorax. The incidence of pneumothorax is 1 percent with this technique and much higher in inexperienced hands.A pneumothorax must be suspected when there is dyspnoea, cough or pleuritic chest pain but the diagnosis can be confirmed only by chest x-ray.

Phrenic nerve block

Phrenic nerve block occurs in 40-60% of patients because of spread of local anaesthetic to the anterior surface of anterior scalene muscle. The effect is avoided if anaesthetic is deposited deep on the middle trunk on division or cord. This is rarely symptomatic. Radiographic confirmation may be obtained.

Recurrent laryngeal nerve block

It causes transient dysphonia, occurs in 1% of case and only on the right side because recurrent laryngeal nerve loops around the subclavian artery on the right side and arch of aorta on the left.

Nerve damage or neuritis

It results from the needle trauma or faulty positioning of anaesthetised arm

preoperatively. Other remote causes include excessive tourniquet time, concentrated solution with vasoconstrictor and susceptible host tissue.

Horner's syndrome

It consists of ptosis, miosis, anhydrosis and enophthalmos. It usually follows stellate ganglion block. It is found in 10% of cases, after interscalene block.

Toxic reaction to drug

It is likely to occur if there is over dosage of drug or inadventent intravascular injection is made, but can be avoided with proper negative aspiration test before drug injection

PHARMACOLOGY OF MIDAZOLAM[13,14,15,16]

Midazolam is a water soluble benzodiazepine. It was first synthesized by Fryer and Walser in 1976. It was the first benzodiazepine that was produced primarily for use in anaesthesia.It is associated with a low incidence of injection pain and post injection phlebitis and thrombosis. It has replaced diazepam as the most commonly administered benzodiazepine in the perioperative period for preoperative medication and intravenous "conscious" sedation. The five principal pharmacologic effects are: sedation, anxiolysis, anticonvulsant actions, spinal cord-mediated skeletal muscle relaxation and anterograde amnesia.

Chemistry :

The molecular weight is 362 with a pKa of 6.2. The parenteral solution used clinically, is buffered to an acidic pH of 3.5. This is important because Midazolam exhibits a pH dependent ring opening phenomenon in which the ring remains open at pH values of less than 4, thus maintaining water solubility of the drug.This water solubility results in a low incidence of injection pain and venous thrombosis. The ring closes at pH values of more than 4, as when the drug is exposed to physiologic pH, thus converting Midazolam to a highly lipid soluble drug.Midazolam is the most lipid soluble benzodiazepine currently available.

Chemical structure :

Midazolam has a fused imidazole ring that is different from classic benzodiazepines. The imidazole ring accounts for the basicity, stability of an aqueous solution and rapid metabolism. It is named 8-chloro-6(2-flurophenyl)-1-methyl-4H- imidazo-(1, 5-α) (1, 4) benzodiazepine maleate. Reversible ring opening of midazolam above and below a pH of 4; the ring closes at a pH> 4, converting midazolam from a water soluble to a lipid soluble drug.

pH DEPENDENT RING OPENING OF MIDAZOLAM

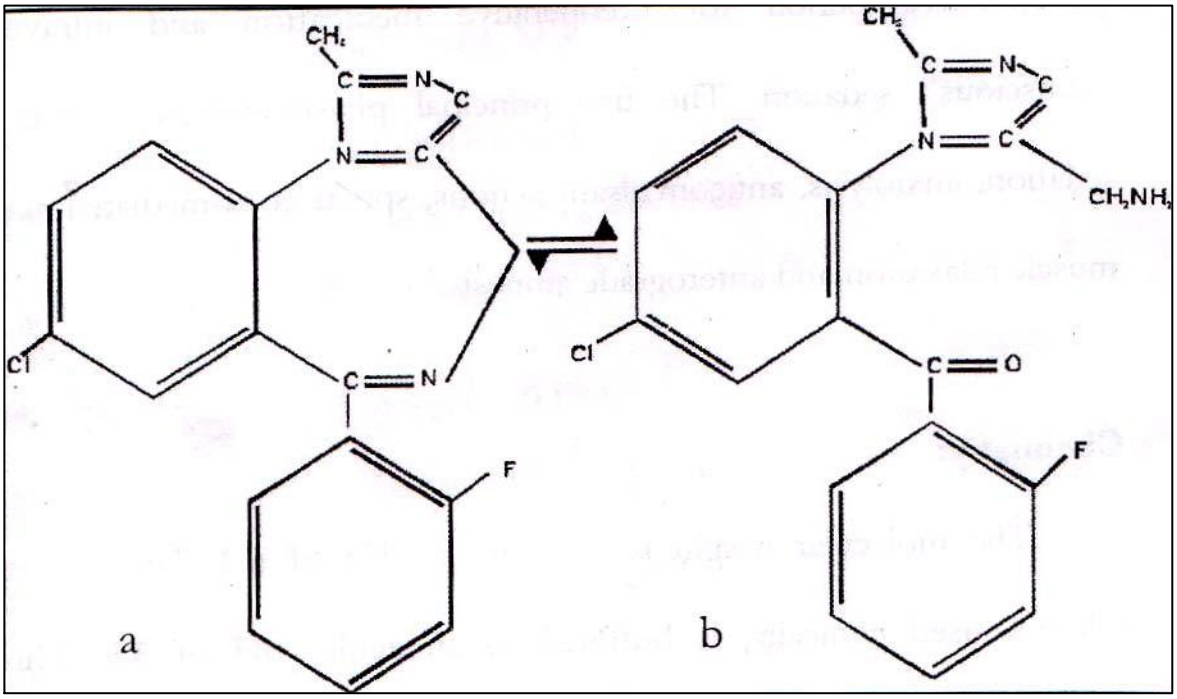


Fig. 7 : Reversible ring opening of Midazolam above and below a pH of 4; the ring closes at a pH> 4, converting Midazolam from a water soluble to a lipid soluble drug.

a. **The active lipid soluble ring configuration in blood.**
b. **The inactive water soluble configuration open ring.**

Mechanism of action :

Midazolam and benzodiazepines in general appear to produce all their pharmacologic effects by facilitating the actions of gamma amino butyric acid (GABA), the principal inhibitory neurotransmitter in the CNS. GABA-adrenergic neurotransmission counterbalances the influence of excitatory neurotransmitters. The benzodiazepine receptors are found in highest densities in the olfactory bulb, cerebral cortex, cerebellum, hippocampus, substantia nigra and inferior colliculus. Current data suggests a pentameric protein composed of 2α, 2β, and 1γ subunits; the proposed arrangement of subunits is arbitrary. (Fig. 8 A)

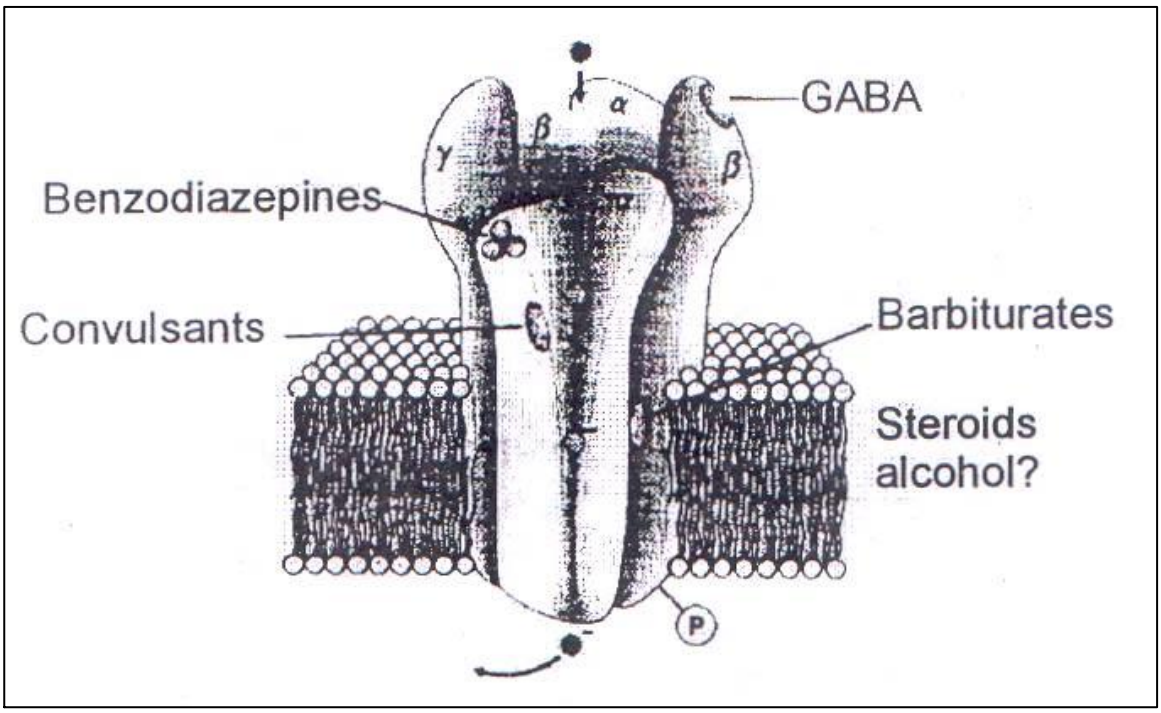
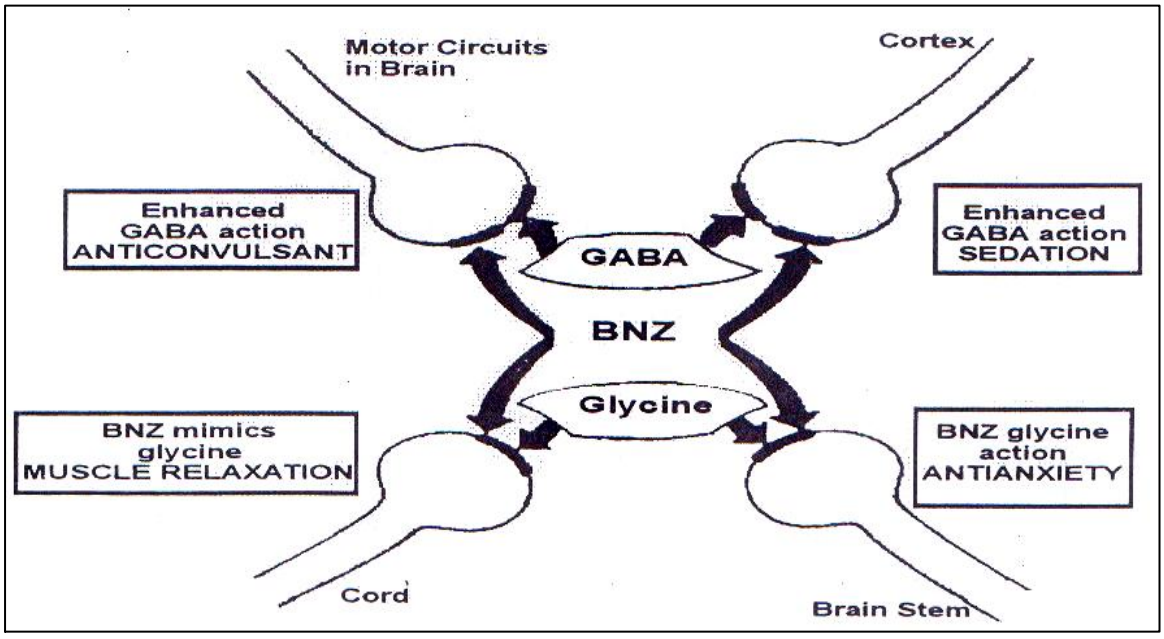


Fig. 8A : Schematic model of the GABA$_A$ receptor complex illustrating recognition sites for many of the substances that bind to the receptor.

The GABA type A ($GABA_A$) is a receptor complex consisting of up to five glycoprotein subunits. When the $GABA_A$ receptor is activated, transmembrane chloride conductance increases, resulting in hyperpolarization of the postsynaptic cell membrane and functional inhibition of the postsynaptic neuron. Midazolam binds to a specific receptor site that is a part of the $GABA_A$ receptor complex. The binding increases the efficiency of the coupling between the GABA receptor and the chloride ion channel. (Fig. 8 B)

BNZ FACILITATES INHIBITORY ACTIONS OF GABA



BNZ MIMICS INHIBITORY ACTIONS OF GLYCINE

Fig. 8B: Mechanisms and sites of action of benzodiazepines

Pharmacokinetics :

Midazolam blood levels decrease rapidly because of its high hepatic clearance, relatively shorter elimination half life (t1/2 ®) and rapid redistribution from the brain to inactive tissue sites. The termination of action after single doses is caused both by distribution into peripheral tissues and by metabolic biotransformation. The context- sensitive half time is shorter when compared to other benzodiazepines with a slow effect-site equilibrium time. It undergoes extensive hydroxylation by hepatic microsomal oxidative mechanisms and the water soluble metabolites are excreted in urine as glucoronide conjugates. Less than 0.5% is excreted unchanged in the urine. First pass metabolism is high. Clearance is also sensitive to hepatic blood flow.

Table A : Pharmacokinetics of Midazolam

Distribution half life (t½ 〈)	7 – 15 minutes
Elimination half life (t½ ®)	1.7 – 2.6 hours
Protein binding	94%
Clearance	6.4 – 11 $ml.kg^{-1}. min^{-1}$
Distribution volume at steady state (Vd_{SS})	1.1 – 1.7 L/kg

Metabolism :

Midazolam undergoes extensive hydroxylation by hepatic microsomaloxidative mechanisms (cytochrome p-4503A4, p4503A3 and p4503A5) to form α- hydroxymidazolam, the principal metabolite and small amounts of 4-hydroxymidazolam and even smaller amounts of 1,4-dihydroxymidazolam (Fig. 4).These water soluble metabolites are excreted in urine as glucoronide conjugates.Very little (< 0.5%) unchanged midazolam is excreted by the kidneys. Plasma concentrations accumulate over the first 30 minutes after administration and reach the highest concentration in the first 2 hours.

Excretion :

Less than 1% of midazolam is excreted unchanged by the kidney. The metabolities are conjugated with glucoronic acid and all are excreted as glucoronides.The principal excretory product is the α-hydroxymethylmidazolam glucoronides.

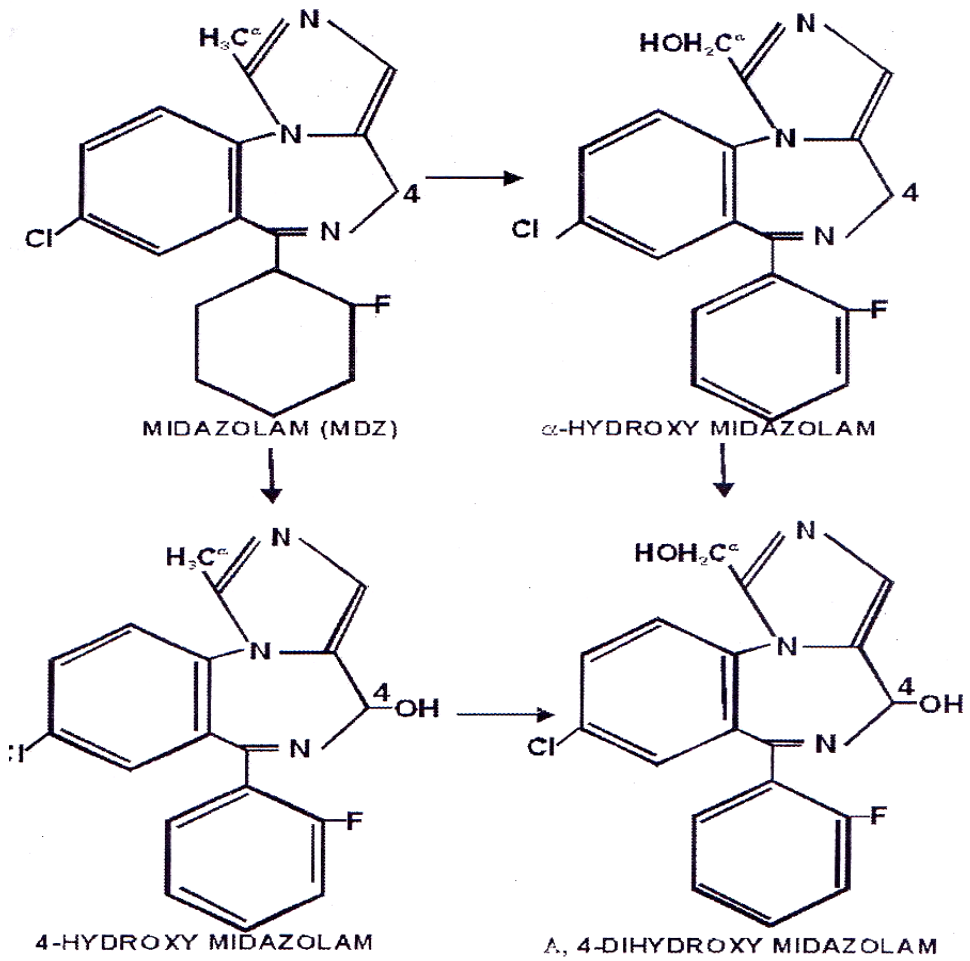


Fig. 9 : Metabolism of Midazolam, with α-hydroxy midazolam occurring in the greatest quantity. All the hydroxylated metabolites are quickly excreted via the kidneys.

Pharmacodynamics :

Increasing plasma concentrations correlate with clinical effects. Assessment of effects are carried out progressively as a steady state is achieved. The half life of equilibrium between plasma concentration of midazolam and its maximal EEG effect is only 2-3 minutes, the time within which sedation is apparent. The therapeutic window to maintain unconsciousness with midazolam is reported to be 100-200 ng/ml with awakening occurring at plasma concentration below 50 ng/ml.

Effects on organ systems :

Central nervous system : Midazolam like other benzodiazepines is a sedative-hypnotic and anxiolytic. It has been suggested that a BZD receptor occupancy of 20% provides anxiolysis, while 30-50% receptor occupancy is associated with sedation and greater than 60% receptor occupancy is required for hypnosis (unconsciousness).It decreases in a dose related manner both cerebral metabolic rate for oxygen($CMRO_2$) and cerebral blood flow (CBF) maintaining a relatively normal ratio of CBF to $CMRO_2$. In patients with intracranial pathology, it decreases cerebral perfusion pressure (CPP) with little effect on intracranial pressure (ICP). It is also a potent anticonvulsant.Midazolam when administered orally, causes anterograde amnesia. Anterograde amnesia generally persists for 20-40 minutes after IV injection of a single dose. The ability to produce a short period of anterograde amnesia is a useful feature of the efficacy of midazolam when used as a sedative for endoscopy and in dentistry. The mild muscle-relaxant property of these drugs is mediated at the spinal cord level, not at the neuromuscular junction.

Respiratory system : Midazolam produces dose dependent respiratory depression. In a dosage of 0.15 mg/kg,Midazolam significantly reduces the ventilatory response to CO_2. In healthy patients,with small iv doses of midazolam 10.075 mcg/kg, the respiratory depression associated with

premedication is insignificant. However, the depressant effect is enhanced with chronic respiratory disease, and synergistic depressant effects occur when it is co-administered with opioid analgesics. Benzodiazepines also depress the swallowing reflex and decrease upper airway reflex activity. Transient apnea may occur after rapid injection of large doses of midazolam (> 0.15 mg/kg IV).

Cardiovascular system : The predominant hemodynamic change is an increase in heart rate and moderate reduction in arterial blood pressure, resulting from a decrease in systemic vascular resistance. The mechanism by which midazolam maintains relatively stable haemodynamics involves the preservation of homeostatic reflex mechanisms. However the cardiovascular depressant effects are frequently "masked" by the stimulus of laryngoscopy and intubation. The myocardial oxygen demand is markedly decreased but there is no alteration of myocardial contractility. There is also a decreased left ventricular end diastolic pressure (LVEDP), reflecting a decreased preload.Coronary vascular resistance is not altered. Coronary perfusion pressure is decreased, as reflected in a minimal fall in diastolic artery pressure. Conclusion is that good stability is observed. Systolic and diastolic blood pressure and pulse rates are not significantly altered.

Other effects :

- Attenuates stress related epinephrine increase, which is minimal.
- Plasma cortisol levels decrease from approximately 12.5 to 7.5 μg/ml
- Adrenocorticotropic hormone (ACTH) changes are minimal.
- Decreases intraocular pressure

Clinical uses :

Midazolam is the most commonly used benzodiazepine for preoperative medication in pediatric patients, IV ("conscious") sedation and induction of anaesthesia. It is also used for maintenance of anaesthesia along with other drugs, and as an anticonvulsant.

	DOSAGE	ROUTE
Induction	0.15-0.40mg/kg	i.v
Maintainence	0.25-1mcg/kg/min	i.v
Premedication	0.07-0.10 mg/kg	i.m
	0.25-0.5 mg/kg	oral
	0.2-0.3 mg/kg	nasal
I.v sedation	0.35mg/kg	Rectal
	0.05-0.15mg/kg	i.v

1. **Preoperative medication :**

- Oral midazolam 0.5 mg/kg 30 minutes before induction provides reliable sedation and anxiolysis in children without producing delayed recovery.
- Intramuscular – 0.05 – 0.1 mg/kg is also effective but less well accepted by children.
- Transmucosal (sublingual) midazolam is as effective as and better accepted than intranasal route in dose of 0.2 mg/kg.
- Jet injection (i.e. using compressed gas instead of a needle) 0.10-0.15 mg/kg produces effective and rapid sedation in children without emotional trauma associated with needle injections.

2. Intravenous sedation : Midazolam in doses of 0.05mg/kg IV is effective for sedation during regional anaesthesia as well as for brief therapeutic procedures. Compared with diazepam, it produces a more rapid onset, with greater amnesia and less post-operative sedation. Pain on injection and subsequent venous thrombosis are less likely with midazolam as it is water soluble.

3. Induction of anaesthesia : Midazolam is the benzodiazepine of choice for use in anaesthetic induction which is defined here as unresponsiveness to command and loss of eyelash reflex. In appropriate doses induction occurs less rapidly than with thiopental but the amnesia is more reliable. Usual

induction dose is 0.1 to 0.4mg/kg or lesser (0.05 – 0.15 mg/kg) in premedicated patients or when co-induced with other agents such as opioids, thiopental or propofol.

4. Maintenance of anaesthesia : It is a useful hypnotic-amnesic during maintenance of general anaesthesia but cannot be used alone for the same. It is used with opioids, propofol and or inhaled anaesthetics. MAC of volatile anaesthetics are decreased in a dose dependent manner. It can also be used as an infusion in a dose of 0.25-1 μg/kg/min.

5. As an anticonvulsant for the treatment of grandmal seizures which may occur with systemic toxicity produced by local anaesthetics.

6. Conscious sedation : Midazolam is probably the only sedative to produce a true state of "conscious sedation". It provides relief of anxiety and anterograde amnesia when administered prior to

- Dental or minor surgical procedures
- Upper GI endoscopy
- Bronchoscopy
- Cardiac surgery
- Critically ill patients in ICU.

Adverse effects :

- Benzodiazepines are remarkably safe drugs in doses routinely used
- Most significant problem with midazolam is respiratory depression when the drug is given for conscious sedation.
- When used as sedatives or for induction and maintenance of anaesthesia, they can produce an undesirable degree or prolonged interval of post operative amnesia, sedation and rarely respiratory depression. The residual effects can be reversed with flumazenil.
- Rarely loss of head control and balance, blurred vision and dysphoria may be seen.

Drug interactions :

- Alcohol, narcotics, sedatives and volatile anaesthetic agents potentiate CNS and circulatory depressant effects.
- Erythromycin, ranitidine, diltiazem, fluconazole, grape fruit juice, verapamil and roxithromycin, increase serum levels and toxic effects.
- Serum levels are decreased by carbamazepine, phenobarbitone, phenytoin and rifampicin.
- It decreases MAC for volatile agents
- Effects are antagonized by flumazenil.

Precautions :

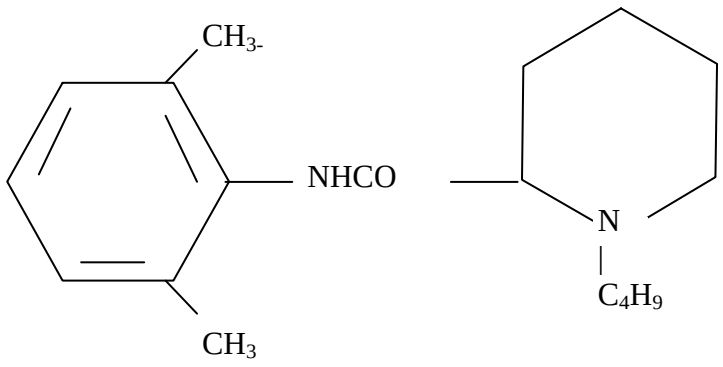
- Reduce the dose in elderly, hypovolemic, high risk patients, and with concomitant use of other sedatives or narcotics.
- COPD patients are unusually sensitive to the respiratory depressant effect.
- It is contraindicated in acute narrow angle or open angle glaucoma.
- It is excreted in human milk, therefore caution should be exercised when it is administered to a nursing woman.

PHARMACOLOGY OF BUPIVACAINE[16,17,18]

Source : Bupivacaine was synthesised by A.F. Ekenstam and his collegues in Sweden in 1957.

Chemistry : The molecular weight of the chloride salt is 325 and that of the base form is 288. It has a melting point of 258^0C. Solutions containing epinephrine have a pH of about 3.5.The chemical name is 1-n-butyl-DL-piperidine-2 carboxylic acid-2, 6 dimethylamilide hydrochloride.

The molecular formula is $C_{18}N_2OH_{28}HCl$.



Chemical structure

Derived from mepivacaine which has a methyl group on the piperidine N_2 atom of the molecule.Addition of a butyl group to piperidine N_2 atom of mepivacaine forms bupivacaine.Bupivacaine is 3.5 times more lipid soluble and 2.4 times more potent than mepivaciane

Bupivacaine Hydrochloride is available in sterile isotonic solutions with and without epinephrine (as bitartrate) 1:200,000 for injection via local infiltration, peripheral nerve block, and caudal and lumbar epidural blocks. Solutions of bupivacaine hydrochloride may be autoclaved if they do not contain epinephrine. Solutions are clear and colorless.

Bupivacaine is related chemically and pharmacologically to the aminoacyl local anesthetics. It is a homologue of mepivacaine and is chemically related to lidocaine. All three of these anaesthetics contain an amide linkage between the aromatic nucleus and the amino, or piperidine group. They differ in this respect from the procaine-type local anesthetics, which have an ester linkage.Bupivacaine Hydrochloride Injection USP is available in sterile, isotonic solutions containing bupivacaine hydrochloride in water for injection with characteristics as follows:

Table-B :Bupivacaine Hydrochloride Injection, USP (without epinephrine)

Concentration	**Bupivacaine Hydrochloride (mg/mL)**	**Sodium Chloride mg/mL**
0.25%	**2.5**	**8.6**
0.5%	**5**	**8.1**
0.75%	**7.5**	**7.6**

May contain sodium hydroxide and/or hydrochloric acid for pH adjustment.

Multiple-dose vials contain methylparaben 1 mg/mL added as a preservative. Bupivacaine and Epinephrine Injection, USP is available in sterile, isotonic solutions containing Bupivacaine hydrochloride and epinephrine 1:200,000 with characteristics

Table-C : Bupivacaine and Epinephrine Injection, USP

Concentration (Bupivacaine HCL)	Bupivacaine Hydrochloride (mg/mL)	Epinephrine 1:200,000 (mcg/mL)	Sodium Chloride (mg/mL)
0.25%	**2.5**	**5**	**8.5**
0.5%	**5**	**5**	**8.5**
0.75%	**7.5**	**5**	**8.5**

Sodium metabisulfite 0.1 mg/mL added as antioxidant and edetate calcium disodium,anhydrous 0.1 mg/mL added as stabilizer. May contain sodium hydroxide and/or hydrochloric acid for pH adjustment .Multiple dose vials contain methylparaben 1 mg/mL added as a preservative. Single-dose solutions contain no added bacteriostat or anti-microbial agent and unused portions should be discarded after use

Physiochemical properties :

1) **Solubility :** The base is sparingly soluble, but the hydrochloride is readily soluble in water.
2) **Stability and sterilization :** Bupivacaine is highly stable and can withstand repeated autoclaving.
3) **pH of saturated solution :** 5.2
4) **Specific gravity :** 1.021 at 37^0C
5) **Pka :** 8.1

6) **Protein Binding :** 95%

7) **Volume of Distribution :** 73 litres

8) **Clearance :** 0.47 litres

9) **Half – life :** 210 minutes

10) **Toxic plasma concentration >** 3mcg/ml

USES

1)Spinal anaesthesia

2) Epidural anaesthesia

3)Caudal anaesthesia

4)Combined Spinal Epidural anaesthesia

5)Peripheral Nerve Block

Anaesthetic properties :

Potency :

Bupivacaine is approximately three to four times more potent than lidocaine.The duration of action of its motor blockade is two to three times longer than lidocaine.

Pk :

Weak base pK_a > physiological pH. At a pH of 7.4, 17% of bupivacaine exists as non-ionised form

Placental Transfer:

Plasma protein binding influences the rate and degree of diffusion of local anesthetics across the placenta . bupivacaine, which is highly protein bound (approximately 95%), has an umbilical vein-maternal arterial concentration ratio of about 0.32. Acidosis in the fetus, which may occur during prolonged labor, can result in accumulation of local anesthetic molecules in the fetus (ion trapping).

Distribution:

Rapid distribution phase (α)– In this phase,the drug gets distributed to highly vascular region.$t_{1/2}$ of α – 2–7 mins

Slow disapparence phase(β)– Drug distributes to slowly equilibrating tissues.$t_{1/2}$ of β – 28 mins

Clearance : 0.47 mmol/min

Dosage and preparation available :

The dosage of Bupivacaine depends on :

- Area to be anaesthetized
- The vascularity of the tissue to be blocked
- The number of neuronal segments to be blocked
- Individual tolerance
- Technique of local anaesthesia

These doses may be repeated in 3-4 hours. 3 mg/kgmg is the maximum dose. The addition of vasoconstrictor produces a very slight increase in the duration of action. However the peak blood level is significantly reduced, there by minimizing the systemic toxicity.

ACTIONS :

Central nervous system :

Overdose of bupivacaine produces light headedness and dizziness followed by visual and auditory disturbances such as difficult to focus and tinnitus. Disorientation and drowsiness can also occur. Shivering, muscular tremors and tremors of muscles of face and distal part of extremities can occur. Ultimately generalized tonic clonic convulsions occurs. Further increase in doses causes respiratory arrest. Since bupivacaine is a potent drug, smaller doses can cause rapid onset of toxic symptoms when compared to other drugs.

Autonomic nervous system :

Bupivacaine does not inhibit the Noradrenaline uptake and hence has no sympathetic potentiating effect. Myelinated preganglionic beta fibres have a faster conduction time and are more sensitive to the action of local anaesthetics including bupivacaine. Involvement of preganglionic sympathetic fibres is the cause of widespread vasodilatation and consequent hypotension that occurs is epidural and paravertebral block.

When used for conduction blockade, all local anaesthetics particularly bupivacaine produce higher incidence of sensory than motor fibres blockade.

Neuro-muscular junctions :

Bupivacaine like other local anaesthetics can block motor nerves if present in sufficient concentration but has no effect on the neuromuscular junction as such.

Cardiovascular system :

The primary cardiac electrophysiologic effect of local anaesthetic is a decrease in the maximum rate of depolarization in the purkinje fibres and ventricular muscle. This is due to a decrease in the availability of sodium channels.Bupivacaine decreases cardiac output by decreasing sympathetic tone,decreasing heart rate and decreasing venous return.It also decreases central venous pressure.There is an increase in blood flow to lower limb with decrease in DVT.

Bupivacaine is highly arrythmogenic. The cardiac contractility is reduced, this is by blocking the calcium transport. Low concentration of bupivacaine produces vasoconstriction while higher doses causes vasodilatation.

Respiratory system :

Respiratory depression may be caused if excessive plasma level is reached. Respiratory depression may also be caused by paralysis of respiratory muscles as may occur in high spinal or total spinal anaesthesia.

Pharmacodynamics :

The onset of action of bupivacaine is between 4 and 6 minutes maximum anaesthesia is obtained between 15 and 20 minutes. The duration of anaesthesia varies according to the type of block, the average duration for peridural block is about 3.5-5 hours, for nerve blocks, it is about 5 to 6 hours.

Toxicity :

The toxic plasma concentration is set at 4-5μg/ml. Maximum plasma concentration rarely approach toxic levels. Non specific local irritant effects on nerve tissue have been noted in human subjects. No evidence of permanent damage has been found in clinical dosage.

Pharmacokinetics :

Bupivacaine can be detected in the blood within 5 minutes of infiltration or following either epidural or intercostal nerve blocks. Plasma levels are related to the total dose administered. Peak levels of 0.14 to 1.18 μg/ml were found within 5 minutes to 2 hours after the administration of anaesthesia and they gradually declined to 0.1 to 0.34μg/ml by 4 hours.

Plasma binding :

In plasma, drug binds avidly with protein (α1- acid glycoprotein) to the extent of 70-95%. The rank order of protein binding for this and its homologues is- bupivacaine< mepivacaine< lidocaine. Conversely, the unbound active fraction is one seventh that of lidocaine and one fifth that of mepivacaine.

Metabolism :

Because bupivacaine is an amide, the liver is the primary site of metabolism. The drug is metabolized partly by N-dealkylation primarily to pipecolyloxylidine. N-disbutyl-bupivacaine and 4-hydroxy-bupivacaine are also formed. It crosses the placental barrier as any other local anaesthetic by passive diffusion, but the lowest level of placental diffusion is reported for this drug (umbilical vein/maternal ratio is 0.31 to 0.44). The high protein binding capacity of the agent is probably the reason why less diffusion occurs across the placenta. No effects on fetus have been noted.

Excretion:

About 10% of drug is excreted unchanged in urine within 24 hours; 5% excreted as pipecolyloxylidine. Glucoronide conjugate is also excreted.

Adverse reactions :

Adverse reactions occur with excessive plasma levels which may be due to overdose, inadvertent IV injections or slow metabolic degradation. These manifest by effects on CNS and CVS. The CNS effects are characterized by excitation or depression. The first manifestation may be nervousness, dizziness, blurring of vision or tremors following drowsiness, convulsions unconsciousness and probably respiratory arrest.

Other effects may be nausea, vomiting, chills, constriction of pupils and tinnitus. The CVS manifestations include myocardial depression, hypotension and cardiac arrest, in obstetrics fetal bradycardia may occur. Allergic reactions include urticaria, bronchospasm and hypotension.

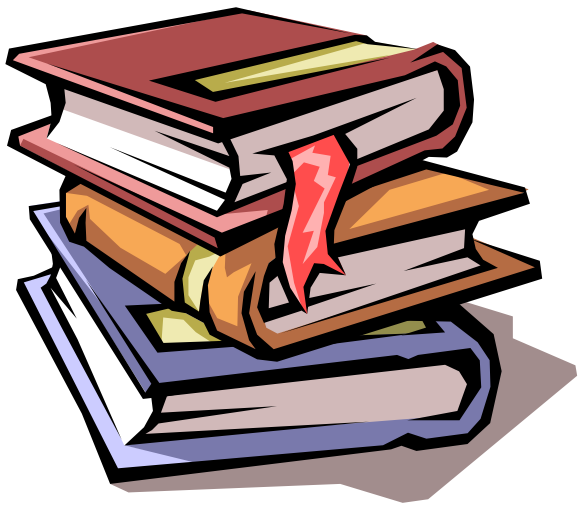
Treatment of adverse reaction :

Treatment is mainly symptomatic. After initiation of basic life support and the ACLS protocol ,a rapid bolus of Intralipid 20%, 1.5 mL/kg (or roughly 100 mL in adults), be administered without delay, followed if necessary by an infusion of 0.25 mL/kg/min for the next 10 minutes. (recommendation of Weinberg and colleagues). Clinicians should make a routine practice of having the following ready at hand: monitoring equipment; an oxygen tank or wall oxygen outlet; airway equipment, including at minimum, a bag-mask circuit for delivery of positive-pressure ventilation; and drugs to terminate convulsions, such as midazolam, lorazepam, diazepam, or thiopental. Treatment of

ventricular fibrillation and tachycardia by amiodarone (5mg/kg iv) or defibrillation (2-6 joule/kg).

Cardiovascular collapse / CNS ratio :

The CC/CNS dose ratio for Bupivacaine is 3.7 ± 0.5 or findings indicating that 3 times drug was required to induce irreversible cardiovascular collapse as was needed to produce convulsions. It has also been suggested that some of the enhanced cardiac toxicity of Bupivacaine is due to greater myocardial uptake.



Review of Literature

REVIEW OF LITERATURE :

1. Edwards et al[19] **(Anaesthesiol 1990;73:273-7)** conducted a randomised control study in rats to find out the mechanism by which midazolam causes spinally mediated analgesia.In this study the electrical current thresholds for pain (ECTP) in the skin of the neck and tail were measured with chronically implanted subarachnoid catheters. Segmental analgesia following midazolam was attenuated ($P<0.05$) when the selective GABA antagonist bicuculline was given intrathecally at the same time as midazolam. The highest dose of bicuculline used, caused no significant attenuation of the segmental analgesic effects of either fentanyl or ketocyclazocine. They concluded that segmental analgesia produced by intrathecal midazolam is mediated by benzodiazepine–GABA receptor complex that is involved in other benzodiazepine actions.

2. Batra YK et al[20] **(Int. Journal Clinical Pharmacol 1999;37:519-23)** conducted a randomised double blinded control study to find out the effect of intrathecal midazolam added to bupivacaine for knee arthroscopy.In this study, 30 healthy patients of ASA-I and ASA-II scheduled for knee arthroscopy were divided into two groups of 15 each.Group M received Inj.midazolam-bupivacaine mixture (midazolam 50mcg/kg+bupivacaine (0.5%)17.5gm/3.5ml) .Group B received Inj.bupivacaine(0.5%) alone (bupivacaine 17.5gm/3.5ml) intrathecally. They recorded the level of sensory

block, sedation score, assessment of pain using visual analogue score in both groups at regular time intervals. Time to block regression, recovery to ambulation and ability to void were recorded and noted before discharged.

A significantly higher Visual Analogue score ($P < 0.05$) was seen in group B. All patients in group B received rescue analgesia at a mean duration of 258 ± 4.68 minutes where as only one patient in group M required supplemental analgesia within this period. Time to regression of sensory analgesia was longer in group M ($P< 0.05$). Neither motor block nor time to void were prolonged with the addition of midazolam to bupivacaine. They concluded that addition of intrathecal midazolam to bupivacaine provides better postoperative analgesia without prolonging motor blockade.

3. Kim M, Lee Y et al [21] – British Journal 2001:86:77-79

A double blind study was conducted to evaluate the post-operative analgesic effects of intrathecal midazolam with bupivacaine following haemorrhoidectomy. 45 patients were randomly allocated to one of the three groups. The control group received 1ml of 0.5% heavy bupivacaine plus 0.2ml of 0.9% saline intrathecally, group BM1 received 1ml of 0.5% bupivacaine plus 0.2ml of 0.5% preservative free midazolam and group BM2 received 1ml of 0.5% bupivacaine plus 0.4 ml of 0.5% midazolam. Time to first analgesia was significantly greater in the midazolam groups than in the

placebo and significantly less in BM1 group than in BM2 group. They concluded that intrathecal midazolam increased the analgesic effects of spinal blockade with bupivacaine.

4. Tucker A P et al [22] **(Anaesthesia Analgesia 2004; 98:1521-7)** conducted a prospective double blind study to evaluate the ability of intrathecal midazolam to increase the potency and duration of the analgesic effects of intrathecal fentanyl, without producing adverse effects. 30 parturients of ASA I and ASA II with cervical dilatation 2-6cm were randomized to receive either intrathecal midazolam 2mg, fentanyl 10μg or both combined to initiate analgesia. Pain scores were recorded before and at 5-min intervals for 30 min after the injection and then every 30 min until the patient requested further analgesia. The presence and severity of nausea, emesis, pruiritus, headache and sedation, in addition to arterial blood pressure, heart rate, respiratory rate, sensory changes to ice, motor impairment, cardiotocograph and apgar score were also recorded.They concluded that intrathecal midazolam potentiated the analgesic effect of fentanyl. It did not increase the occurence of any maternal adverse events or abnormalities on the cardiotocography.

5. Yokoyama et al [23] **in 1998 (Canadian journal of Anaesthesia 1998;45:551-5)**conducted a prospective randomised controlled study was

conducted to investigate the effect of midazolam on epidural infusion of bupivacaine. 60 patients of ASA I and ASA II scheduled for gastrectomy were divided into 3 groups of 20. The following mixtures, in 40 ml, were infused continuously over 12 hours after surgery; 40ml bupivacaine 0.5% in group C, bupivacaine 0.5% 38ml + 10mg midazolam in group M10 and bupivacaine 0.5% 36 ml + 20mg of midazolam in group M20. Better analgesia was obtained in patients receiving midazolam than in group C ($P < 0.05$). Frequency of rescue analgesics administration was greater in group C ($P < 0.05$). Greater sedation was seen in groups M10 and M 20 during first 120 minutes without any respiratory depression, which was desirable in the postoperative period. They concluded that adding midazolam to a continuous epidural infusion of bupivacaine provides better analgesia and sedation than bupivacaine alone without side effects in patients undergoing laparatomy.

6. Nishiyama et al [24] **(J Clinical Anaesthesia 2002;14(2):92-97)** conducted a prospective randomized double-blinded study to investigate the interaction of midazolam with different doses of bupivacaine, by comparing the analgesic, sedative and amnesic effects of continuous epidural midazolam with two different does of bupivacaine. 100 ASA I and II post gastrectomy patients without any complications were divided in 4 groups (n = 25) and administered thoracic epidural infusion (40 ml / 12 hour) of the drugs via a balloon infuser.

The contents of the infuser (40ml) were bupivacaine, 180mg with midazolam 20mg (HM group), bupivacaine, 90mg with midazolam 20mg (LM group), bupivacaine, 180mg without midazolam (HC group) and bupivacaine, 90mg without midazolam (LC group). It was found that HM group had significantly better analgesia and sedation. The time to the first rescue medication was longest in HM group followed by LM, then HC and finally LC groups. The number of patients with amnesia were greater in HM and LM groups. They concluded that adding midazolam increased not only the analgesic but also the sedative effect with increasing dose and bupivacaine in a post operative continuous epidural administration.

7.Mahajan R,Batra YK, [25] Int J Clin Pharmacol Ther2001;39(3):116-20

A double-blinded study was designed to evaluate the analgesic efficacy of caudal midazolam- bupivacaine combination in providing post-operative pain relief in children undergoing genito-urinary surgery and to study the occurence of side effects . Thirty children, aged 2 to 8 years, scheduled for genito-urinary surgery were allocated randomly to receive either 0.25% bupivacaine 0.5 ml/kg (group B; n = 15) or 0.25% bupivacaine 0.5ml/kg with 50 μg/kg midazolam (group BM; n = 15) by caudal route immediately after induction of general anaesthesia. Lowest pain scores were observed with the addition of midazolam to caudal bupivacaine ($p < 0.01$). Duration of analgesia was longer

in group BM (11 ± 0.5h) as compared to group B (7.4 ± 2.1h) ($p < 0.05$). No significant changes in heart rate, blood pressure and oxygen saturation was observed. The authors concluded that caudal administration of midazolam – bupivacaine mixture prolongs post-operative analgesia compared to bupivacaine alone without any adverse effects.

8. Culebras X, Van Gessel [4] (Anaesth Analg 2001;92:199-204)

A prospective randomized double blinded study was conducted to determine the efficacy and adverse effects of clonidine,when mixed with a long acting local anaesthetic on postoperative analgesia. 60 adult patients of ASA I and II undergoing rotator cuff repair under interscalene brachial plexus block were included in the study. The study group received 150μg of clonidine with 40ml of 0.5% heavy bupivacaine. It was found that duration of analgesia was unaltered but the mean arterial pressure and heart rate were significantly decreased in clonidine group. They concluded that clonidine,as an adjuvant in brachial plexus block does not improve post operative analgesia but does induce haemodynamic changes.

9. Morris M.E et al[27] (Brain Res 1983;278(1-2):117-26) conducted a randomised controlled study in which the inhibitory neurotransmitter GABA has been shown to have a depolarizing action on myelinated axons of both mammalian and amphibian peripheral nerves. In initial in-vivo observations

intravenous injections of GABA caused an increase in excitability of the low threshold fast conducting fibres of the superficial radial and median nerves of cat. Similar, graded, reversible effects were confirmed (using changes in the amplitude / integral of the stimulus evoked A fiber submaximal compound action potential to assess excitability) in in-vitro studies with the isolated, desheathed frog sciatic nerve. GABA caused a mean maximal increase in half-maximal action potential of 29.8% (S.E. ± 2.7), with an ED50 value of 0.09 mM and hill coefficient of 0.70.. They concluded that extrasynaptic receptors of GABA are present on myelinated axons of peripheral nerves

10. Jarbo K et al [28] (Canadian journal of anaesthesia 2005 :52:822-6) conducted a prospective randomized double blind study to assess the effect of midazolam added to brachial plexus block.This study was conducted on 40 ASA I and II adult patients undergoing upper limb surgeries under supraclavicular brachial plexus block.. Patients in group B (n = 20) were administered 30ml of 0.5% bupivacaine and group BM (n = 20) were given 30ml of 0.5% bupivacaine with midazolam 50μ/kg.Haemodynamic variables (i.e., heart rate, noninvasive blood pressure), pain scores and rescue analgesic requirements were recorded for 24 hr postoperatively. The onset time and duration of sensory and motor blockade were recorded. The onset of sensory block was significantly faster in group BM (12±2.9 mins) when compared to group B (20±3.8).This result was statistically significant (P < 0.05).

The onset of motor block was significantly faster in group BM (9.2 ± 2.38 mins) when compared to group B (17.1±3.83).This result was statistically significant($P < 0.05$). The duration of motor blockade was not different in two groups .In Group B, the duration of motor blockade was 5.1 ± 1.14 while in Group BM,the duration of motor blockade was 5.6±3.32. This result was statistically insignificant ($P > 0.05$). Pain scores were significantly higher in group B compared to group BM from two hours to 24 hrs postoperatively ($P < 0.05$). Rescue analgesic requirements were significantly less in group BM compared to group B ($P < 0.05$). Haemodynamics and sedation scores did not differ between groups in the postoperative period. They concluded that Midazolam (0.05mg/kg) in combination with 30ml of bupivacaine (0.5%) hastened onset of sensory and motor block, and improved postoperative analgesia in brachial plexus block, without producing any adverse effects.

11. Naguib M et. al [29](Can J Anaesthesia 1995;42:758-64) conducted a randomized double-blinded study,in which they compared the efficacy of midazolam with bupivacaine for caudal analgesia in children undergoing inguinal herniotomy. They were allocated randomly into three groups (n = 15 in each) to receive a caudal injection of either 0.25% bupivacaine 1 ml/kg with or without midazolam 50 μg /kg or midazolam 50 μg/ kg with normal saline 1 ml/kg. There were no differences in quality of pain relief, postoperative behaviour or analgesic

requirements between the midazolam group and the other two groups. Times to first analgesic administration (paracetamol suppositories) were longer ($P < 0.001$) in the bupivacaine-midazolam group than in the other two groups. Further, the bupivacaine-midazolam group received fewer ($P < 0.05$) doses of paracetamol suppositories than the bupivacaine group. Side effects such as motor weakness, respiratory depression or prolonged sedation were not observed in patients who received caudal epidural midazolam only. They concluded that caudal midazolam in a dose of 50 μg /kg provides equivalent analgesia to bupivacaine 0.25% of 1ml/kg when administered postoperatively in a volume of 1 ml/kg for children following unilateral inguinal hemiotomy.

12 . Nishikawa K ,Kanaya N,Nakayama M [30] **(Anaesth Analg 2000;91(2):384-7** conducted a double-blind study to evaluate the effect of fentanyl added to lidocaine for axillary brachial plexus block in 66 adult patients of ASAI & II scheduled for elective hand and forearm surgeries. The duration of sensory blockade was significantly increased in fentanyl group (323 ± 96 min) as compared to the control (250 ± 79 min)group. However the onset time of sensory blockade was prolonged , due to decreased pH of fentanyl.

13. R Hickey, Joan Hoffman et al [31] **(Anaesthesiology 74:639-342, 1991)** conducted a double blind study to compare the efficacy of 0.5% ropivacaine and 0.5% bupivacaine for brachial plexus block.48 patients received a subclavian perivascular brachial plexus block for upper extremity surgeries. One group

received(n=24) 0.5% plain ropivacaine 175mg and second group received (n=24) 0.5% plain bupivacaine 175mg . The block was performed using Winnie's technique by eliciting paresthesia. Sensory block, motor block , duration of analgesia, duration of anaesthesia and side effects were evaluated. They concluded that ropivacaine and bupivacaine 0.5% were equally effective in providing brachial plexus block in the onset and duration of motor and sensory block, incidence of adverse events and the need for supplementation with rescue analgesics.

14. Gulec et al [32]**(European Journal of Anaesthesiol 1998;15:161-5)** conducted a prospective double blind randomised control study to find out the efficacy of bupivacaine-midazolam mixture to bupivacaine – morphine mixture to prolong post-operative analgesia in caudal block.In this study,60 children undergoing inguinal or urogenital surgery were randomly divided into three groups of 20 each.Group I received caudal injection of bupivacaine 0.125% 0.75ml/kg with midazolam 50 mcg/kg.Group II received Inj.bupivaciane 0.125% with Inj. 1% morphine 0.05 mg/kg.Group III received Inj.bupivacaine 0.125% alone.There were no significant changes in heart rate,blood pressure,respiratory rate or oxygen haemoglobin saturation.There were no significant differences in the incidence of vomiting and pruritis between the groups($P>0.05$).Sedation scores were higher in bupivacaine-morphine group and bupivacaine-midazolam group($P<0.01$).The durations of analgesia were 21.15$\pm$ 1.2 hrs in bupivacaine-midazolam group,14.50$\pm$ 1.6 hrs in bupivacaine-morphine group and 8.15$\pm$ 1.3 hrs in

bupivacaine group.The difference between plain bupivacaine and bupivacaine-midazolam group was statistically significant(P<0.001),bupivacaine-midazolam and bupivacaine-morphine group was also significant(P<0.01).They concluded that caudal administration of bupivacaine-midazolam mixture produces a longer duration of post-operative analgesia than bupivacaine-morphine or bupivacaine alone with sedation for 8-12 hours.

15.Serraro J M et al [33] **(Pain 1992;48:5-12)** conducted a prospective, double blind, randomised and dummy-controlled trial in 28 patients with chronic mechanical low back pain presenting to the York Pain Clinic. The therapeutic effects of epidural methyl prednisolone (80 mg) were compared with intrathecal midazolam (2 mg). The two groups of patients were comparable in terms of pain duration, demography, extent of disability, anxiety and depression and pain locus of control. The pain was assessed before and for 2 months after treatment using the short form McGill Pain Questionnaire as well as visual analogue and verbal rating scales for sensory and affective components of their pain experience..They found out that all the patients treated with steroid were taking more or the same amount of self-administered analgesic medication during the 2 month follow-up period. But one-half of midazolam-treated patients took less medication during the 2 month follow-up period. They concluded that intrathecal midazolam is an effective treatment for chronic mechanical low back pain.

16.Shaikh S et al[34] **(Anaesthesia,Pain and Intensive Care 2012;16(1):7- 11** conducted a prospective, randomized, double blind study to find out the effects of Inj. midazolam added to bupivacaine in supraclavicular brachial plexus block. This study was done in 50 adult patients of ASA I and II, aged between 18-65 years,who were scheduled for various upper limb surgeries. Patients were divided into two groups of 25 each. Group B received 30ml of Inj. bupivacaine 0.5% +2ml normal saline and group BM received 30ml of Inj. bupivacaine 0.5% + inj. midazolam (preservative free) 0.05mg/kg. Patients were observed for sedation, respiratory depression, pulse rate, SBP, DBP, duration of motor block, duration of pain relief and occurrence of any complications.Post operative analgesia was significantly longer (805.04175.75 min) in group BM, as compared to group B (502.2452.68 min) with p value <0.001. Pain score was significantly low in group BM (mean 1.6), compared to group B (mean 4.92) at 12 hours postoperatively. Onset of sensory block was 8.36$\pm$3.58 min and 8.52$\pm$ 4.18 min in group B and group BM respectively with p value >0.05. Hence there was no statistically significant difference. Onset of motor block in group B was 9.96$\pm$5.69 min and in group BM was 7.92 $\pm$5.68 min. and p value was >0.05 min. This was not statistically significant . Mild respiratory depression and sedation occurred intraoperatively in group BM which required no active intervention. In.brachial plexus block, addition of Inj.midazolam 50 mcgs/kg to

30ml of 0.5% bupivacaine improved post operative analgesia and prolonged sensory blockade without producing any adverse effects.

17. Tucker A P et al[35] **(Anaesthesia Analgesia 2004;98:1512-20)** conducted a cohort study which evaluated the potential of midazolam to produce symptoms suggestive of neurological damage.This study compared cohorts of patients who received intrathecal anaesthesia with or without intrathecal midazolam(2 mg).They evaluated eighteen risk factors regarding the symptoms with respect to the potential neurological complications.1100 patients were followed up prospectively during the first postoperative week by a hospital chart review and one month later by a mailed questionnaire. Any symptoms suggestive of neurological impairement,like motor or sensory changes,bladder or bowel dysfunction were evaluated.They found out that intrathecal (2 mg) was not associated with an increased risk of neurologic symptoms in contrast to preclinical studies done in animals.

18. Nishiyama et al[36] **(Anaesthesia Analgesia 1999;89:717-20)** conducted a randomised control study in cats to investigate the acute histopathological effects of intrathecal midazolam.They did the study in 40 cats divided into 2 groups of 20.The first group was given midazolam 10 mg(2ml) and the second group was given saline 2ml.After 1,2,4, or 6 hours after administration,these cats were killed and histology report was examined using light microscopy.Inflammatory changes were only seen in cats in the saline group.In conclusion,upto 6 hrs after direct exposure to midazolam,no inflammatory damage was seen.

19. Vandana Trivedi et al[37] **[J Indian Med Assoc 2010; 108: 563-7]** conducted a study to compare the effects of midazolam and clonidine added to bupivacaine. A randomised controlled clinical trial was conducted for 60 ASA I-II presenting for elective upper limb orthopaedic surgeries of duration of less than120 minutes.They were divided into 2 groups of 30 each, Group C receiving clonidine and Group M receiving preservative free Inj.midazoalm. All were premedicated with injection glycopyrrolate 0.2mg intramuscular 30 minutes before surgery and injection bupivacaine 0.5% plain 20 ml and injection lignocaine 2% plain 10 ml in supraclavicular brachial plexus block. In group C patients injection clonidine 150 mcg and in group M injection midazolam preservative free 5 mg were administered along with local anaesthetics. All the patients were observed for onset and duration of sensory and motor blockade, sedation score, postoperative analgesia with visual analogue scale score up to 12 hours. The mean time for onset of sensory blockade in clonidine group was 6.08 ± 1.67 mins while in midazolam group,was 6.33 ± 0.99 mins,p value was 0.5.51,hence not significant($p>0.05$).The mean time for onset of motor blockade in clonidine group was 9.3 ± 2.02 mins while in midazolam group, was 10.13$\pm$0.89 mins.The p value was found out to be 0.15,hence not significant.The mean duration of motor blockade in group C was found out to be 4.5 ± 0.41 hours while in group M, was 4 ± 0.35 hours,p value was found to be 1.19,hence not significant.The mean duration of sensory blockade was 4$\pm$0.36 hours,while in group M,was 3.5$\pm$0.30.The p value was found to be 1.068,hence not significant. Sedation score

was more in group C(score of 2)when compared to group M(score of 1).Post operative analgesia was more in group C(VAS score of <3 in 300 mins) when compared to Group M (VAS score of > 3 in 300 mins). No complications were observed in any one of patient in both the groups. So injection clonidine provides better postoperative analgesia and more sedation than midazolam.

20. Nasreen Laiq, Mohammad Naeem Khan, Mohammad Arif and Shahid Khan[38] **(Journal of the College of Physicians and Surgeons Pakistan 2008, Vol. 18 (11): 674-678):**This randomised controlled clinical trial was done to compare the onset, duration and postoperative pain scores in supraclavicular block with bupivacaine alone and bupivacaine-midazolam combination**.**This study was conducted in 50 ASA I and II adult patients undergoing upper limb surgeries under supraclavicular block. Patients were randomly allocated into two groups of 25 each.

Group A -30 ml of 0.5% Inj.bupivacaine

Group B were given 30 ml of 0.5% Inj.bupivacaine with midazolam 50 µg/kg. Hemodynamic variables (heart rate, noninvasive blood pressure, oxygen saturation), pain scores, rescue analgesic requirements and sedation score were recorded for 24 hours postoperatively.They found out that the onset of sensory blockade was significantly faster in Group B(14±3.1) when compared to Group A(22±3.5)(P value<0.01)They also found that onset of motor blockade was significantly faster in Group B (10.5±2.40) when compared to Group

A(18.5±3.1)The post-operative analgesia was significantly prolonged in Group B(9.30±4.50)than in group A(6.20±1.8),p value <0.01,hence statistically significant.The duration of motor blockade was significantly prolonged in Group B(7.65±3.20) when compared to Group A(5.20±2.10)The number of rescue analgesics required were also less in group B when compared to group A. Hemodynamics and sedation score were also similar in both the groups.They concluded that addition of Inj.midazolam to bupivacaine in supraclavicaular brachial plexus block fastened the onset of sensory and motor blockade and provided prolonged post operative analgesia without producing any adverse effects.

21. Sibel Baris et al [39] (**Pediatric Anesthesia Volume 13, Issue 2, pages 126 - 131, February 2003)** This randomised control study was conducted to evaluate the intensity and efficacy of 0.75 ml/kg bupivacaine 0.25% with the addition of fentanyl or midazolam for caudal block in children undergoing inguinal herniorrhaphy.In this study, 75 ASA I & II patients were allocated randomly into 3 groups of 25 each Group B –bupivacaine (plain)0.25%, Group BM- bupivacaine-midazolam (50mcg/kg), Group BF- bupivacaine-fentanyl(1mcg/kg) after induction of anaesthesia. Haemodynamic parameters, pain score, additional analgesic requirements and side-effects were noted. The mean systolic arterial pressure at 10, 20, 30 min after caudal block was higher in group B when compared with groups BF and BM. Mean intraoperative heart

rate was lower in group BF than the other groups. Adequate analgesia was obtained in all patients (100%) in group BF, 23 patients (92%) in group BM and 21 patients (84%) in group B ($P > 0.05$), hence not significant. The time to recovery to an aldrete score of 10 was significantly shorter in group B than in group BM ($P < 0.05$). and in group BF(P value>0.05). There was no difference in additional analgesic requirements between the groups in the first 24 h. Sedation score was higher in the BM group at 60 and 90 min postoperatively than the other groups.They concluded that in caudal block, the addition of fentanyl(1 mcg/kg) or midazloam(50mcg/kg) as adjuvants to bupivacaine do not provide any further analgesic requirement when compared to 0.75 ml/kg bupivacaine (0.25%) alone.

22. A.Kharbasfrushan et al[40] (Iranian Red Crescent Med J. May 2012; 14(5): 276–282).This prospective double blind randomised control study was done to assess the effect of intrathecal midazolam to reduce the severity of pain in caesarean section.In this study 124 ASA I and II parturient females were assigned into 2 groups of 62 each. Women in the experimental group received bupivacaine (10 mg) plus intrathecal midazolam (2 mg/ml) (BM) and those in the control group received bupivacaine plus normal saline (BNS).The pain severity was measured using a verbal numerical rating scale.In group BM, the patients had significant pain relief during 15 and 120 mins after surgery.But there was no significant difference during 5,30,60,240 mins after surgery. The average time until the first dose of additional analgesic was 142.18±55.19 min in the BNS vs 178.06±77.33 min in the

BM group. They concluded that combination of bupivacaine (10 mg) plus intrathecal midazolam (2 mg) was an effective anesthetic technique to proI,ide improvement in pain. The onset of sedation was faster in the group that received bupivacaine plus intrathecal midazolam compared with those who received bupivacaine plus normal saline.

Methodology

METHODOLOGY

Study Design : Prospective Single Blinded Case Control Study.

Sample Size : 100 patients

Sampling Method : Randomised sampling

Statistical Analysis : Student's 't' test was used to test the significance of difference between quantitative variables and Yate's chi square test was used for qualitative variables

Method of collection : All patients undergoing elective upper limb surgery

After obtaining approval from the institutional ethical committee, Thanjavur Medical College,Thanjavur, the study was conducted in 100 ASA I or II patients, aged between 15 to 55 years undergoing elective upper limb surgeries under supraclavicular block. Before including the patients for the surgery,all patients were explained about the procedure and written informed consent was taken from the patient and the patient's attenders. Result values were recorded using a preset proforma.

Inclusion criteria :

- ASA CLASS I & II
- Age between 15 to 55 years.
- SBP → 100 – 139mm of Hg.
- DBP → 60 – 89mm of Hg.

Exclusion criteria :

- Patients with a previous history of hypersensitivity to Midazolam
- Patients with medical complications like anemia, uncontrolled diabetes mellitus, liver failure, renal failure,cardiovascular disorders,
- Abnormal BT, CT or on anticoagulant therapy.
- Local infection
- Patient refusal
- Neuromuscular disorders
- Pregnancy
- Nerve injury

Each patient was randomly allocated into one of the two groups of 50 patients each

- Control group – Group-B :Received 30 ml of Inj. bupivacaine (0.375%)
- Study group – Group BM: Received 30 ml of mixture of I n j . bupivacaine (0.375%) and midazolam (2.5 mg)(Preservative free)

Materials:

Sterile tray, sterile swab, sterile towel, sponge holding forceps

Drugs for the block: 0.375% bupivacaine 30 ml and midazolam 2.5 mg(preservative free)

Equipments and drugs for resuscitation and conversion to general anaesthesia in the case of block failure were kept ready.

Methods :

Pre operative preparation:

Patients were preoperatively assessed and ASA risk stratified. Basic investigations like blood grouping/typing, haemoglobin, bleeding/clotting time, blood sugar, renal function test, urine routine, chest x-ray, ECG were done.

All patients were premedicated with Inj. Glycopyrrolate 45 minutes prior to the planned procedure.Peripheral venous line was accessed using a 18G intravenous cannula and all patients were preloaded with 10 ml/kg of Ringer lactate solution just within 30 minutes before performing the suparaclavicular block. Monitor was connected and baseline parameters namely heart rate, blood pressure, SpO2, respiratory rate were recorded.

Patient's position- Patient was laid supine with the head 30 ^{0} turned to the opposite side.The arm on the operative side is adducted, the shoulder is down and the elbow is fixed. A small folded towel was placed below the shoulder at interscapular area to make the field more prominent.

Needle size - 22 gauge, 5 cm needle

Anaesthetic Solution Volume – 30 ml

Anatomic Landmarks- The interscalene groove and mid-point of clavicle,subclavian artery pulsations were identified

Approach and Technique - Identify the interscalene groove.This is often a shallow dimple.Follow the groove down the root of the neck.The subclavian artery is palpable in 50% of the patients in this position.

- After aseptic preparation of area, at a point 1.5 to 2.0cm posterior and cephalad to the mid point of clavicle, subclavian artery pulsations were felt. A skin wheel was raised with local anaesthetic just cephalo-posterior to the pulsations..
- Insert the a 22 gauge, 5 cm needle at the lowest point of the interscalene groove(where the skin is beginning to flatten out over the supraclavicular fossa),in the posterior part of the groove and posterior to the subclavian artery
- The plexus may be identified using either paraesthesia or muscle stimulation
- Using paraesthesia, sensation must be elicited in any area below the shoulder/deltoid.Best results follow paraesthesia in the hand or fingers.However paraesthesia limited thumb alone are associated with apoor block success rate.
- After eliciting paraesthesia,a 10ml syringe was mounted on the needle and after negative aspiration of blood, the study medication was injected.
- All patients were monitored for onset of sensory blockade, motor blockade and for any complications

Assessment Of Sensory Blockade

The sensory scales used for assessment were 4-point scale ,Hollmen's scale.

Hollmen's scale was used to evaluate sensory blockade:

Sensory block was assessed by pin prick with 23g hypodermic needle in skin dermatomes C4-T2 once in every minute for initial 30 minutes and then after every 30 minutes.

1- Normal sensation of pin prick

2- Pinprick felt as sharp pointed but weaker compared to the area in the opposite limb.

3- Pinprick recognised as touch with blunt object.

4- No perception of pin prick

Onset of sensory block was assessed as the time interval between administration of drug and absence of sensation to pin prick.(Hollmen's ≥ 3)

Duration of sensory block was defined as the time elapsed between injection of drug and appearance of pain requiring analgesia was also noted.(Hollmen's scale less than or equal to 1)

Assessment Of Motor Blockade –

The scales used for assessment of motor blockade were Hollmen motor scale,Modified Bromage scale,Lavoie's scale.

Lavoie's criteria was used for evaluation of motor blockade:

Grade 1- 0 – flexion and extension in both the hand and arm against resistance

Grade 2 -33%- flexion and extension in both the hand and arm against gravity but not against resistance

Grade 3- 66%- flexion and extension movements in the hand but not in the arm

Grade 4- 100%- No movement in the entire upper limb

Onset of motor block was assessed as the time interval between administration of drug and loss of flexion/extension movements in the arm.(Lavoie's criteria Grade 3)

Duration of motor block was defined as the time elapsed between injection of drug and complete return of muscle power was also noted(Lavoie's criteria Grade 1)

Sedation score described by Culebras et al [4]was used to assess sedation.

1 – awake and alert

2 – sedated, responding to verbal stimulus.

3 – sedated, responding to mild physical stimulus.

4 – sedated, responding to moderate or severe physical stimulus.

5 – not arousable.

Other sedation scores include Ramsay sedation score,University of Michigan sedation scale,verbal rating score,bispectral index score(BIS score),

OAA/S(Observer's Assessment Alertness/Sedation)

The effect on the following parameters were observed

1) Onset of sensory blockade
2) Onset of motor blockade
3) Duration of sensory blockade
4) Duration of motor blockade
5) Sedation score
6) Haemodynamic variables
7) Number of rescue analgesics given during 24 hours post-operative period.

Success of the block was defined as:

A) **Complete**: Intended surgical procedure being able to be performed with no sedation.

B) **Incomplete**: Intended surgical procedure being able to be performed with minimal sedation. The patient was intraoperatively sedated only after the block was already classified. When required,Inj Pentazocine (0.5 mg/kg), intermittent doses of Inj.Propofol (0.5 mg/kg) and Inj. Ketamine (0.5 mg/kg) was given intravenously to supplement the anaesthesia.

C**) Failed block**: Intended surgical procedure not being able to be perfomed under the block, and requiring conversion to general anaesthesia.

- Heart rate, non-invasive blood pressure and O_2 saturation were also

monitored.

- Number of rescue analgesics in 24 hours of post-operative period was also recorded.

- All patients were monitored for 24 hours post-operatively.

- All patients were given rescue analgesics if they complained of pain or any discomfort

Patients were watched for bradycardia, convulsions, restlessness, disorientation, drowsiness, nausea, vomiting and any other complications

Statistical Tools

The information collected regarding all the selected cases were recorded in a Master Chart.

Data analysis was done with the help of computer using Epidemiological Information Package (EPI 2010) developed by Centre for Disease Control, Atlanta.

Using this software range, frequencies, percentages, means, standard deviations, chi square and 'p' values were calculated. Student's 't" test was used to test the significance of difference between quantitative variables and Yate's chi square test was used for qualitative variables.

A 'p' less than 0.001 was considered to be highly significant.

A 'p' value less than 0.05 was considered to be significant.

Observation And Results

OBSERVATION AND RESULTS

This prospective single blind randomised controlled study was done in 100 ASAI and II of either sex aged between 15-55 years , posted for upper limb surgeries under supraclavicular brachial plexus block.The study was undertaken to evaluate the efficacy of midazolam (2.5mg) as an adjuvant to bupivacaine (0.375%) in comparison with plain bupivacaine (0.375%) for brachial plexus block by supraclavicular approach.

DEMOGRAPHIC DATA

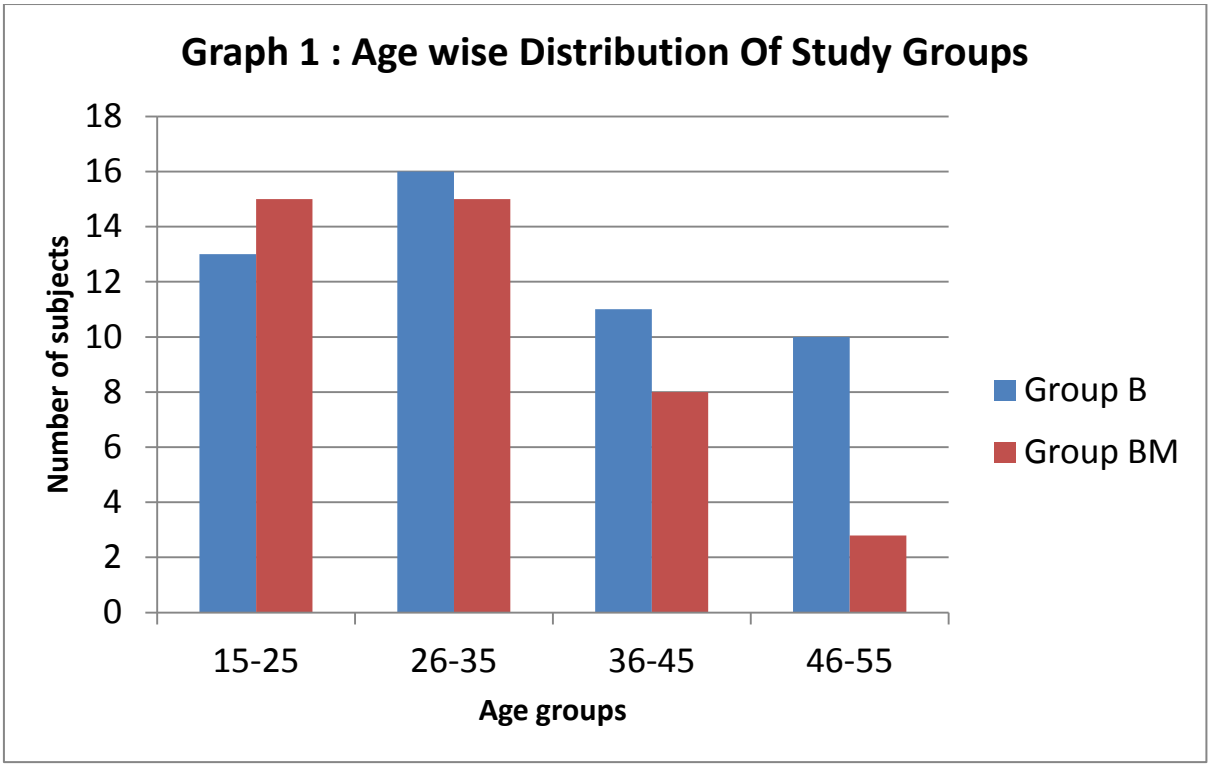
Table 1 : Age-wise Distribution of Study groups

Age in years	Group B		Group BM		t value	p value	Significance
	No.	%	No.	%			
15-25	13	26	15	30	0.216	0.83	Not Significant
26-35	16	32	15	30			
36-45	11	22	8	16			
46-55	10	20	12	24			
TOTAL	50	100	50	100			

Group B : Bupivacaine

Group BM : Bupivacaine – Midazolam

As shown in Table 1 the minimum age of the patient was 15 years and the maximum age was 55 years. The total number of persons in Group B in theage group 15-25 is 13 while in Group BM is 15.The total number of persons in Group B in the age group 26-35 is 16 while in Group BM is 15.The total number of persons in Group B in the age group 36-45 is 11 while in Group BM is 8.The total number of persons in the age group 46-55in Group B is 10 while in Group BM is 12. Samples are age matched with p value which was found out to be 0.83.($p>0.05$),hence statistically not significant.So the age distribution between the two groups were comparable.



Group B : Bupivacaine

Group BM : Bupivacaine – Midazolam

Table 2 : Comparison Of Group B And Group BM On The Basis Of Time For Onset Of Sensory Block (Min)

Study group	Onset time (min)	Mean difference	t* value	p value	Significance
B	19.08 ± 1.7	7.82	24.13	0.0007	HS
BM	11.26 ± 1.5				

* Student's unpaired t test

HS – Highly significant($p<0.001$)

As shown in Table 2 the mean time for onset of sensory block in group BM was 11.26 ± 1.53 min and in group B was 19.07 ± 1.7 min. The statistical analysis by student's unpaired 't'test showed that, the time for onset of sensory block in group BM was significantly faster when compared to group B ($p< 0.001$).

Table 3 : Comparison of Group B and Group BM on the basis of time for onset of motor block (min)

Study group	Onset time (min)	Mean difference	t* value	p value	Significance
B	15.30 ± 2.09	5.74	16.38	0.0009	HS
BM	9.56 ± 1.32				

* Student's unpaired t test

HS – Highly significant ($p<0.001$)

As shown in Table 3 the mean time for onset of motor block in group BM was 9.56 ± 1.32 min and in group B was 15.3 ± 2.09 min. The statistical analysis by unpaired student's 't' test showed that, the time for onset of motor block was significantly faster when compared to group B ($p < 0.001$).

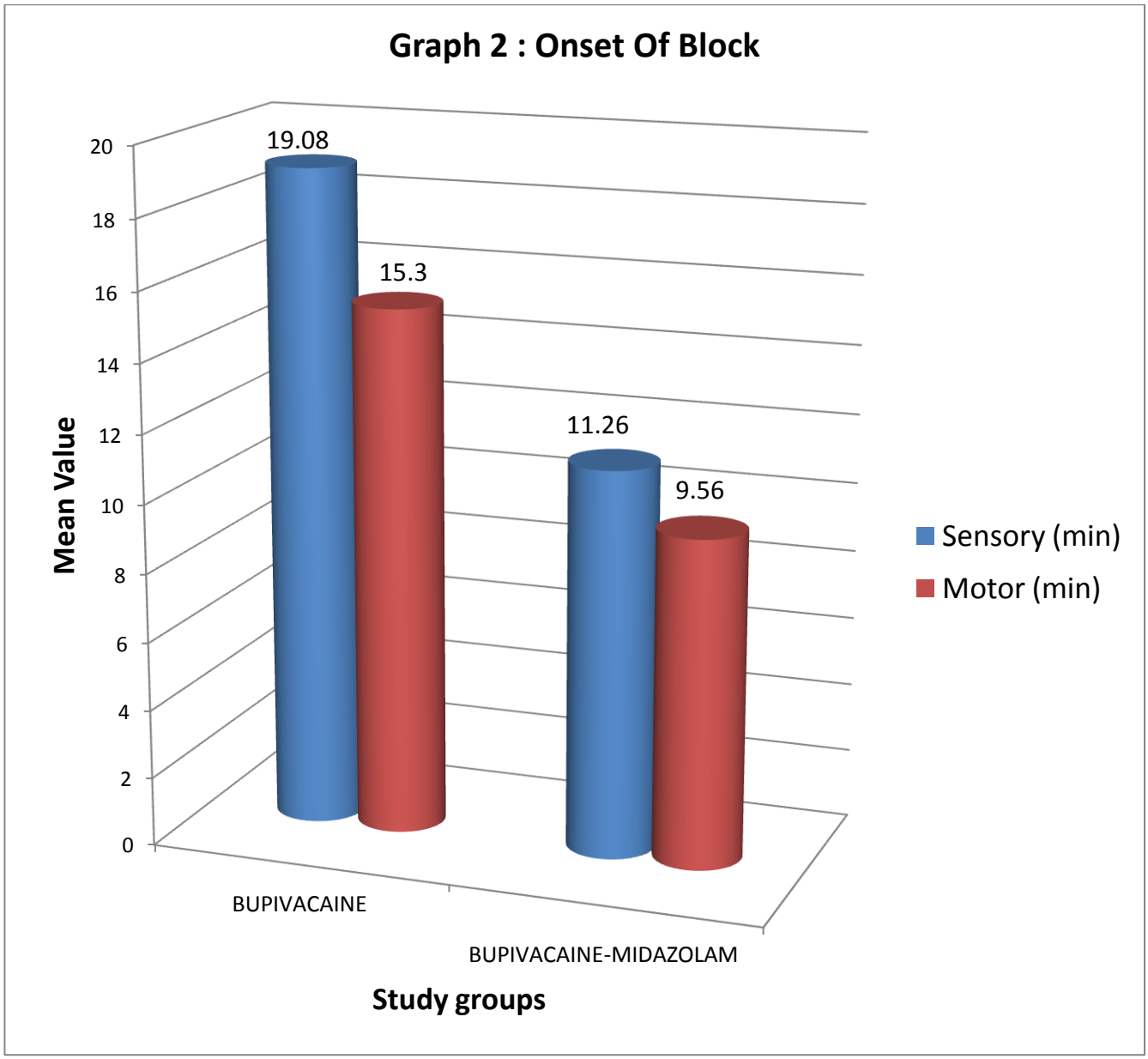


Table 4 : Comparison of Group B and Group BM on the basis of Duration of Sensory Block (hours)

Study group	Duration of block (hrs)	Mean difference	t* value	p value	Significance
B	5.84 ± 0.49	7.96	42.2	0.0003	HS
BM	13.81 ± 1.23				

* Student's unpaired t test

HS – Highly significant($p<0.001$)

As shown in Table 4 patients of both groups were observed for 24 hours. Time was noted when the patient asked for rescue analgesics. The mean duration of sensory block in group BM was 13.81 ± 1.23 hours and in group B was 5.84 ± 0.49 hours. The statistical analysis by students unpaired 't' test showed that the duration of sensory block in group BM was significantly longer when compared to group B ($p < 0.001$).

Table 5 : Comparison of Group B and Group BM on the basis of Duration of motor block (hours)

Study group	Duration of block (hrs)	Mean difference	t* value	p value	Significance
B	5.13 ± 0.45	0.12	1.32	0.12	NS
BM	5.25 ± 0.45				

* Student's unpaired t test NS – Not significant ($p>0.05$)

As shown in Table 5 the mean duration of motor block in group BM was 5.25 ± 0.45 hours and the group B was 5.13 ± 0.45 hours. The statistical analysis by students unpaired 't' test showed that the difference between duration of motor block in group BM and group B was not significant ($p > 0.05$).

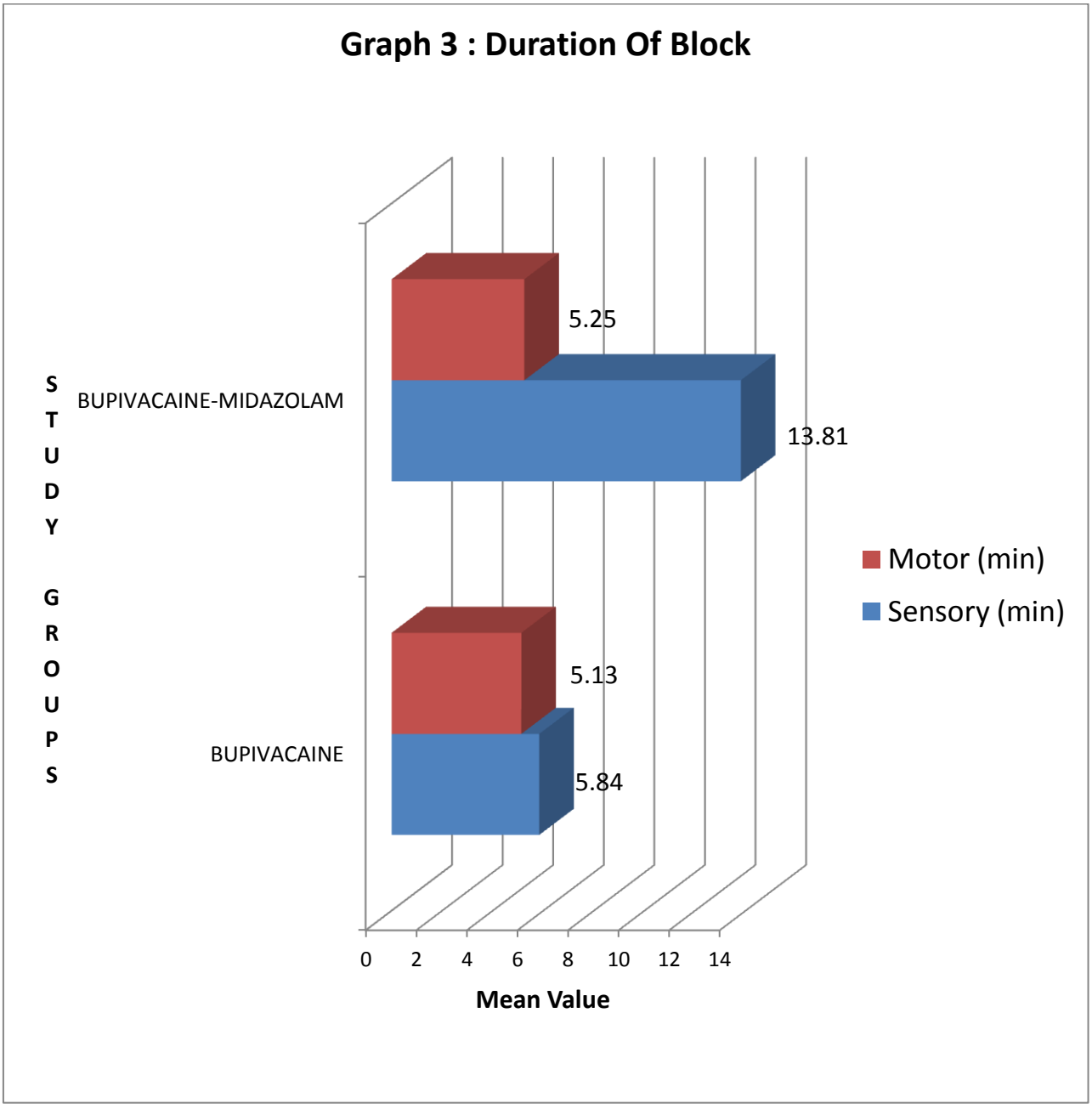


Table 6 : Comparison of Group B and Group BM on the basis of Number of Rescue Analgesics required in 24 hours post-op period

No. of RA in 24 hours post-op	BUPIVACAINE	BUPIVACAINE+ MIDAZOLAM
1	0	37 (74)
2	38 (76)	13 (26)
3	12 (24)	0

χ^2 = 61.25 P= 0.0008 Highly Significant($p<0.001$)

Figures in the parenthesis indicate column wise percentage

As shown in Table 6, in group BM, 74% patients required only 1 rescue analgesic dosage and 26% of patients required 2 rescue analgesic doses in post-op 24 hours. In group B 76% of patients required 2 and 24% of patients required 3 rescue analgesic doses in post-op 24 hours. This difference in number of rescue analgesic doses required by patient of both groups is statistically highly significant by chi-square test (χ^2 = 61.25, $p< 0.001$).

Graph 4 : No. Of Rescue Analgesics Required In 24 Hours Post-Op Period

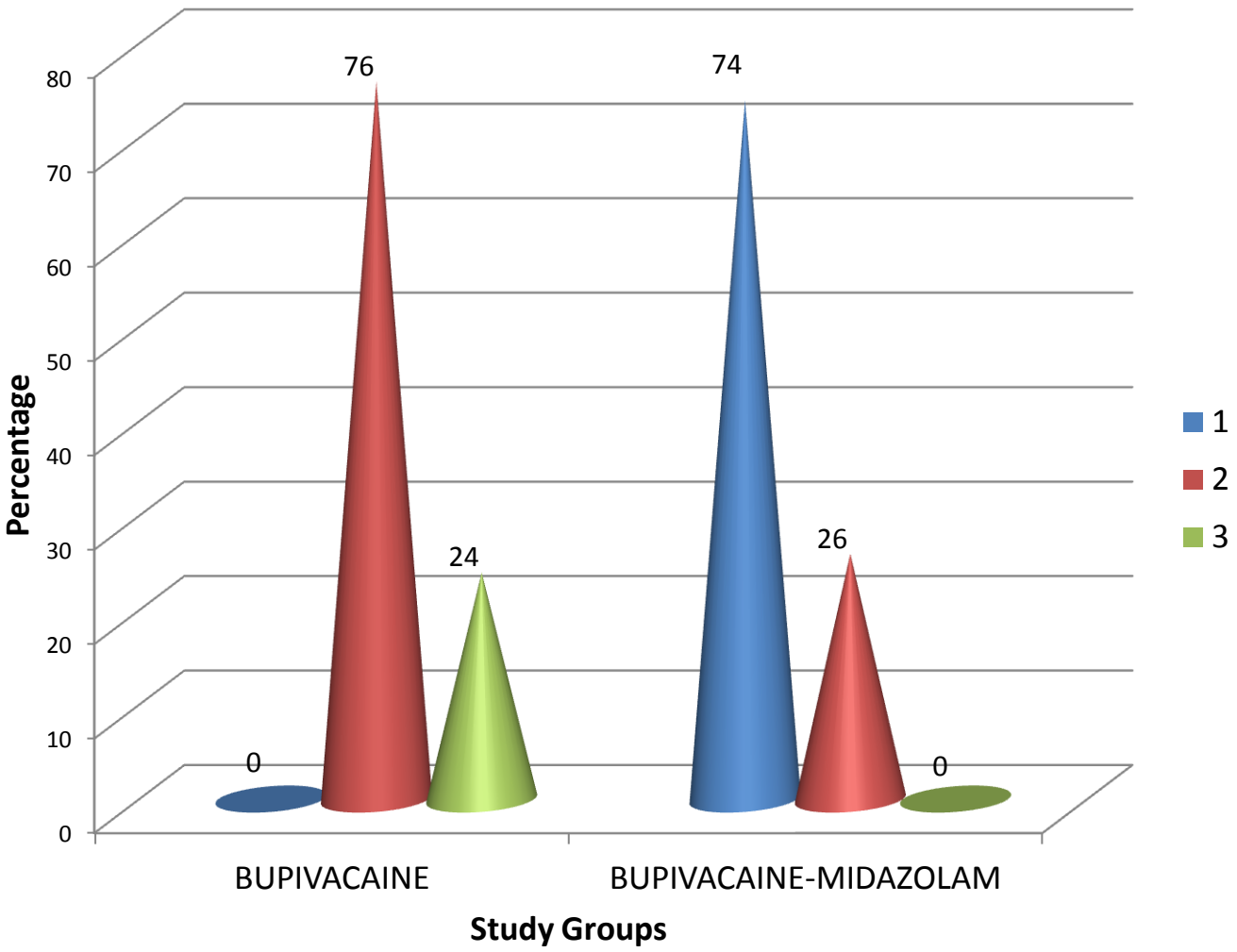


Table 7 : Comparison of Group B and Group BM on the basis of Sedation score

Time of Assessment	Scores	Bupivacaine	Bupivacaine -Midazolam	X^2 Value, p value
0 min	1	50 (100)	50 (100)	-
	2	0	0	-
5 min	1	50 (100)	50 (100)	-
	2	0	0	-
15 min	1	50 (100)	40 (80)	$X^2 = 9.0$
	2	0	10 (20)	$p = 0.01$
30 min	1	50 (100)	34 (68)	$X^2 = 16.74$
	2	0	16 (32)	$p = 0.005$
60 min	1	50 (100)	37 (74)	$X^2 = 12.73$
	2	0	13 (26)	$p = 0.009$
2 hrs	1	50 (100)	50 (100)	-
	2	0	0	-
6 hrs	1	50 (100)	50 (100)	-
	2	0	0	-
12 hrs	1	50 (100)	50 (100)	-
	2	0	0	-
24 hrs	1	50 (100)	50 (100)	-
	2	0	0	-

SEDATION SCORES

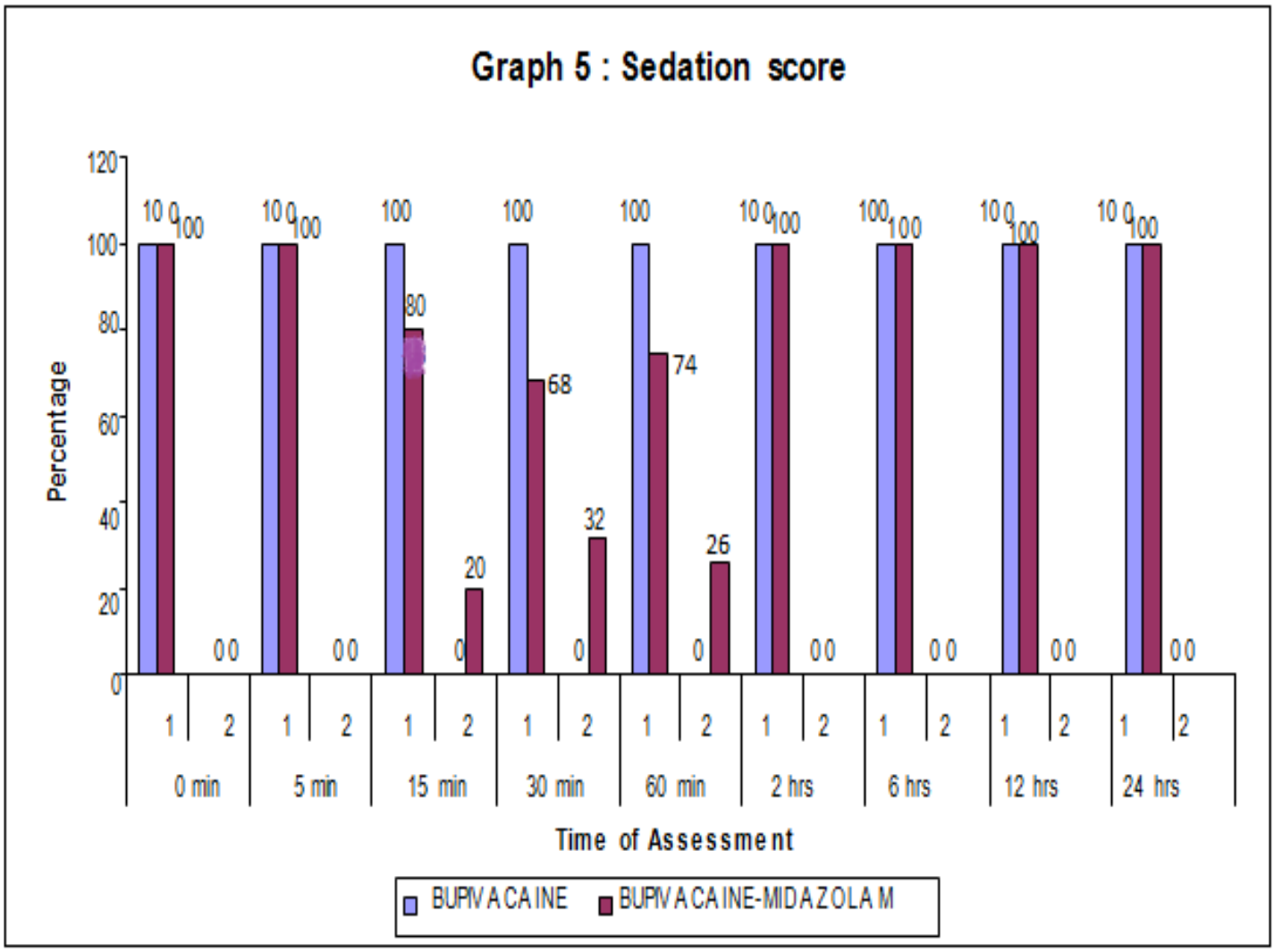
1 – Awake and alert

2 – Sedated, responding to verbal stimulus

3 – Sedated, responding to mild physical stimulus

4 – Sedated, respond to moderate to severe physical stimulus

5 – Not arousable



As shown in Table 7, in group B all patients were awake and alert and had sedation score of 1. In group BM, sedation corresponding to score 2 was observed in some patients between 15 minutes from time of injection to 60 minutes. 20% of patients at 15 minutes, 32% of patients at 30 minutes and 26% of patients at 60 minutes had sedation score of 2. None of the patients had sedation score of 3 and above during the study period. Statistical analysis of sedation score by chi-square test showed that the difference in sedation score was significant ($p < 0.05$) during 15, 30 and 60 minutes

Hemodynamic variables :

Pulse rate, systolic BP, diastolic BP, O_2 saturation was recorded at 0 min, 5 min, 15 min, 30 min, 60 min, 2 hours, 6 hours, 12 hours, 24 hours.

Table 8 : Comparison of Group B and Group BM on the basis of Pulse Rate (beats / min)

Time of Assessment	Mean+/- SD		Mean Difference	t* Value	p Value	Significance
	Bupivacaine	Bupivacaine-Midazolam				
0 min	77 ± 6.8	78 ± 7.4	1.48	1.03	0.18	NS
5 min	77 ± 6.6	78 ± 7.0	1.24	0.91	0.23	NS
15 min	76 ± 7.0	78 ± 7.0	1.44	1.03	0.17	NS
30 min	76 ± 6.6	78 ± 7.4	1.46	1.04	0.16	NS
60 min	77 ± 6.5	78 ± 7.2	1.36	0.99	0.22	NS
2 hrs	77 ± 7.0	78 ± 7.0	1.1	0.79	0.32	NS
6 hrs	77 ± 6.6	78 ± 7.0	1.48	1.05	0.19	NS
12 hrs	76 ± 6.0	78 ± 7.0	2.04	1.49	0.11	NS
24 hrs	77 ± 7.0	79 ± 7.0	1.52	1.09	0.19	NS

* Student's unpaired t test

NS = Not Significant (p value > 0.05)

As shown in Table 8, in group B, the mean pulse rate ranged from 76 ± 6.0 to 77 ± 7.0 beats/ min. In group BM, the mean pulse rate ranged from 78 ± 7.0 to 79 ± 7.0 beats / min. The statistical analysis by student's unpaired 't' test showed that there was no significant difference in pulse rate between the two groups ($p > 0.05$).

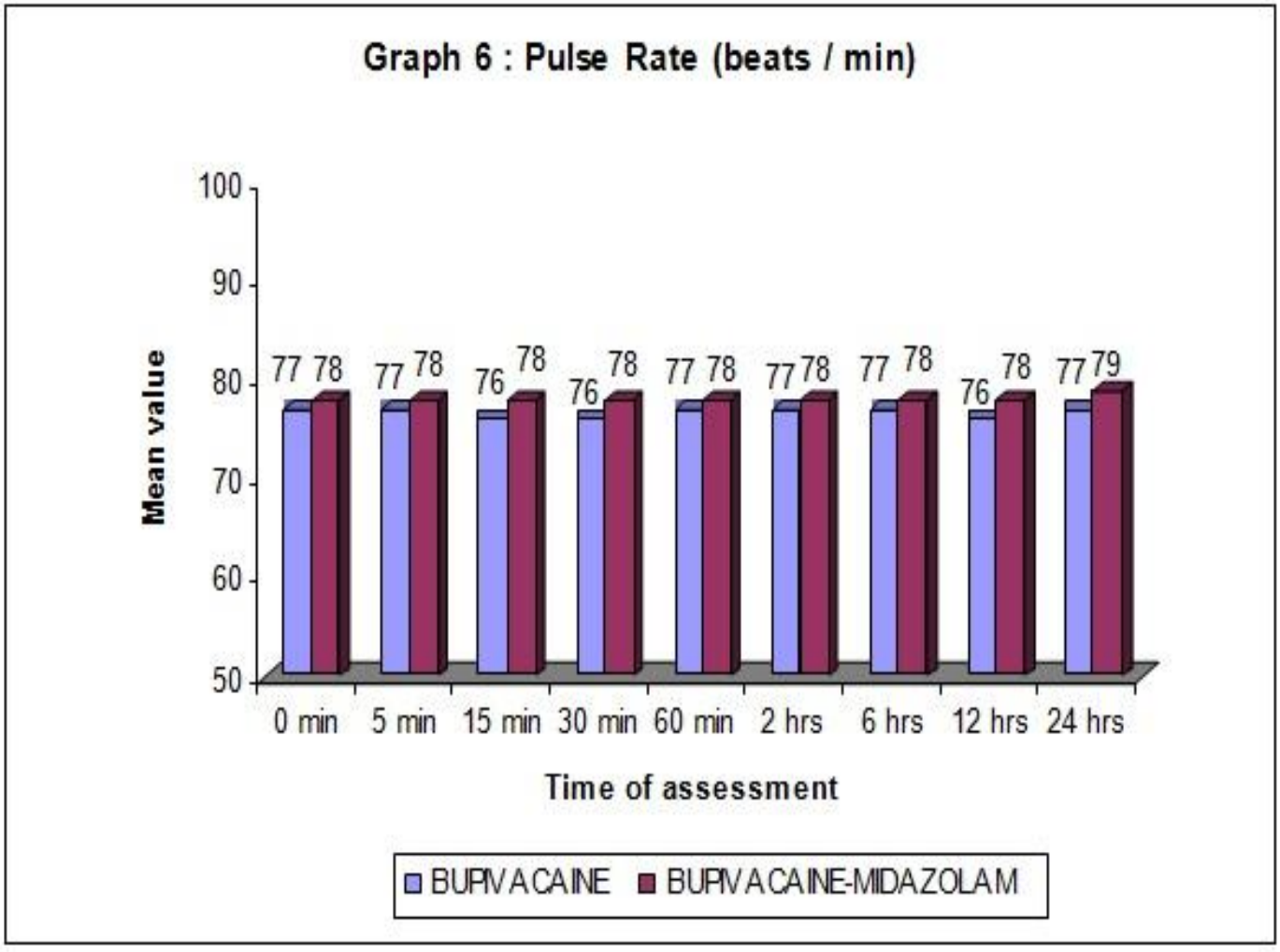


Table 9 : Comparison of Systolic blood pressure (mm of Hg) in Group B and Group BM

Time of Assessment	Mean+/- SD		Mean Difference	t* Value	p Value	Significance
	Bupivacaine	Bupivacaine-Midazolam				
0 min	117 ± 10.45	117 ± 10.53	0.76	0.36	0.62	NS
5 min	118 ± 10.37	117 ± 10.88	0.1	0.047	0.92	NS
15 min	118 ± 010.01	118 ± 10.84	0.08	0.038	0.94	NS
30 min	118 ± 10.38	118 ± 11.01	0.12	0.056	0.91	NS
60 min	118 ± 9.47	117 ± 10.86	0.02	0.01	0.99	NS
2 hrs	117 ± 10.04	118 ± 10.99	0.7	0.33	0.64	NS
6 hrs	117 ± 10.01	118 ± 11.19	0.48	0.22	0.83	NS
12 hrs	117 ± 9.96	118 ± 11.10	0.68	0.32	0.65	NS
24 hrs	117 ± 9.85	118 ± 11.07	1.04	0.49	0.52	NS

* Student's unpaired t test

NS = Not Significant (p >0.05)

As shown in Table 9, in group B, the mean systolic blood pressure ranged from 117 ± 9.85 to 118 ±10.38 mm of Hg. In group BM, the mean systolic blood pressure ranged from 117 ± 10.53 to 118 ± 11.19 mm of Hg. The statistical analysis by unpaired student's 't' test showed that there was no significant difference in systolic blood pressure between the two groups ($p > 0.05$).

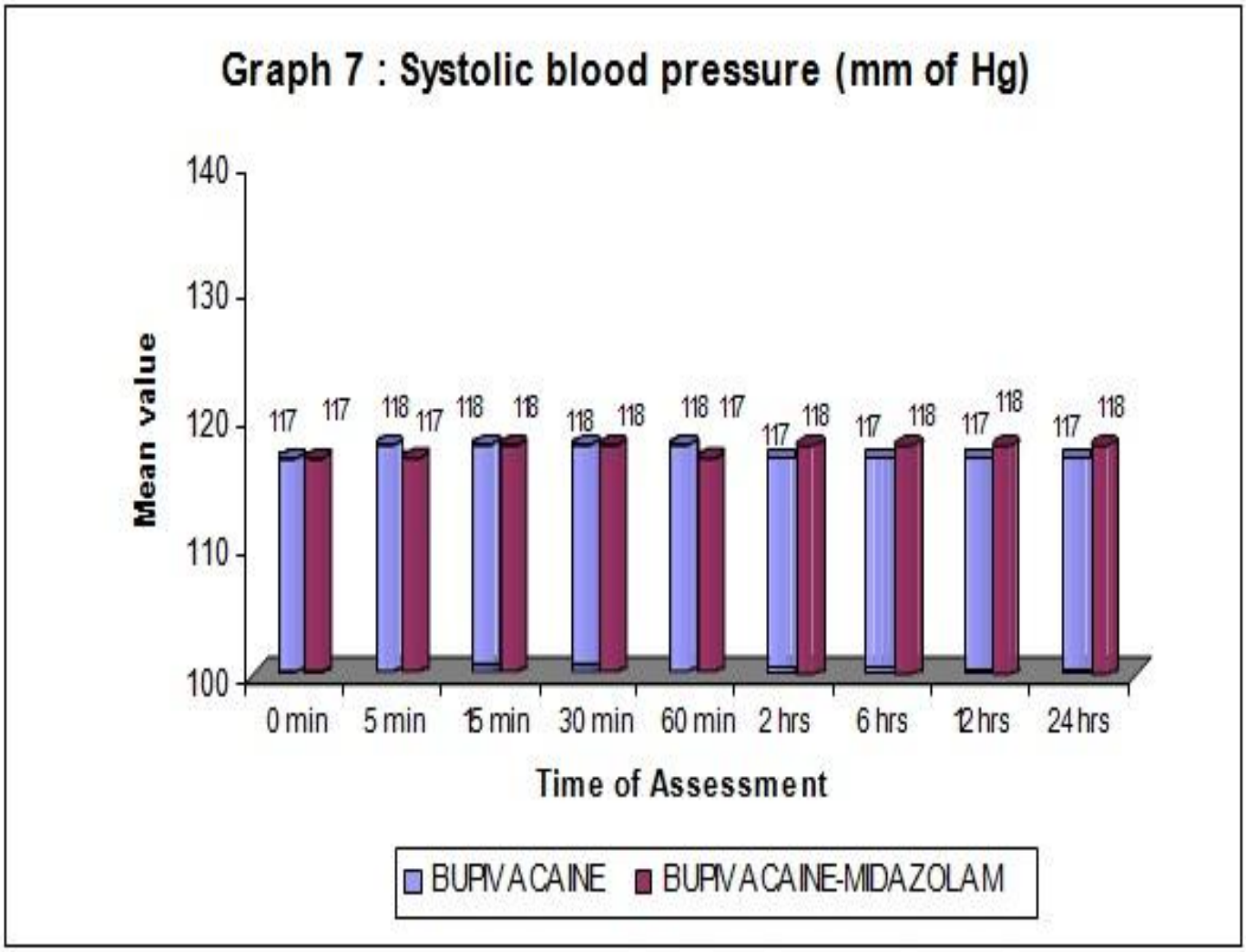


Table 10 : Comparison of Diastolic blood pressure (mm of Hg) in Group B and Group BM

Time of Assessment	Mean+/- SD		Mean Difference	t* Value	p Value	Significance
	Bupivacaine	Bupivacaine-Midazolam				
0 min	76 ± 7.72	77 ± 6.8	0.38	0.26	0.81	NS
5 min	76 ±7.52	77 ± 6.74	1.02	0.71	0.38	NS
15 min	76 ± 7.07	77 ± 6.72	1.14	0.82	0.31	NS
30 min	77 ± 7.10	77 ± 6.85	0.38	0.27	0.79	NS
60 min	76 ± 7.03	77 ± 6.66	0.74	0.54	0.52	NS
2 hrs	76 ± 7.06	77 ± 6.82	0.48	0.34	0.72	NS
6 hrs	76 ± 7.15	77 ± 6.73	0.52	0.37	0.75	NS
12 hrs	76 ± 6.9	77 ± 6.92	0.52	0.37	0.75	NS
24 hrs	76 ± 6.9	77 ± 6.67	0.5	0.36	0.74	NS

* Student's unpaired t test

NS = Not Significant (P>0.05)

As shown in Table 10, in group B, the mean diastolic blood pressure ranged from 76 ± 6.9 to 77 ± 7.1mm of Hg. In group BM, the mean diastolic blood pressure ranged from 77 ± 6.6 to 77 ± 6.9 mm of Hg. The statistical analysis by student's unpaired 't' test showed that there was no significant difference in diastolic blood pressure between the two groups ($p > 0.05$).

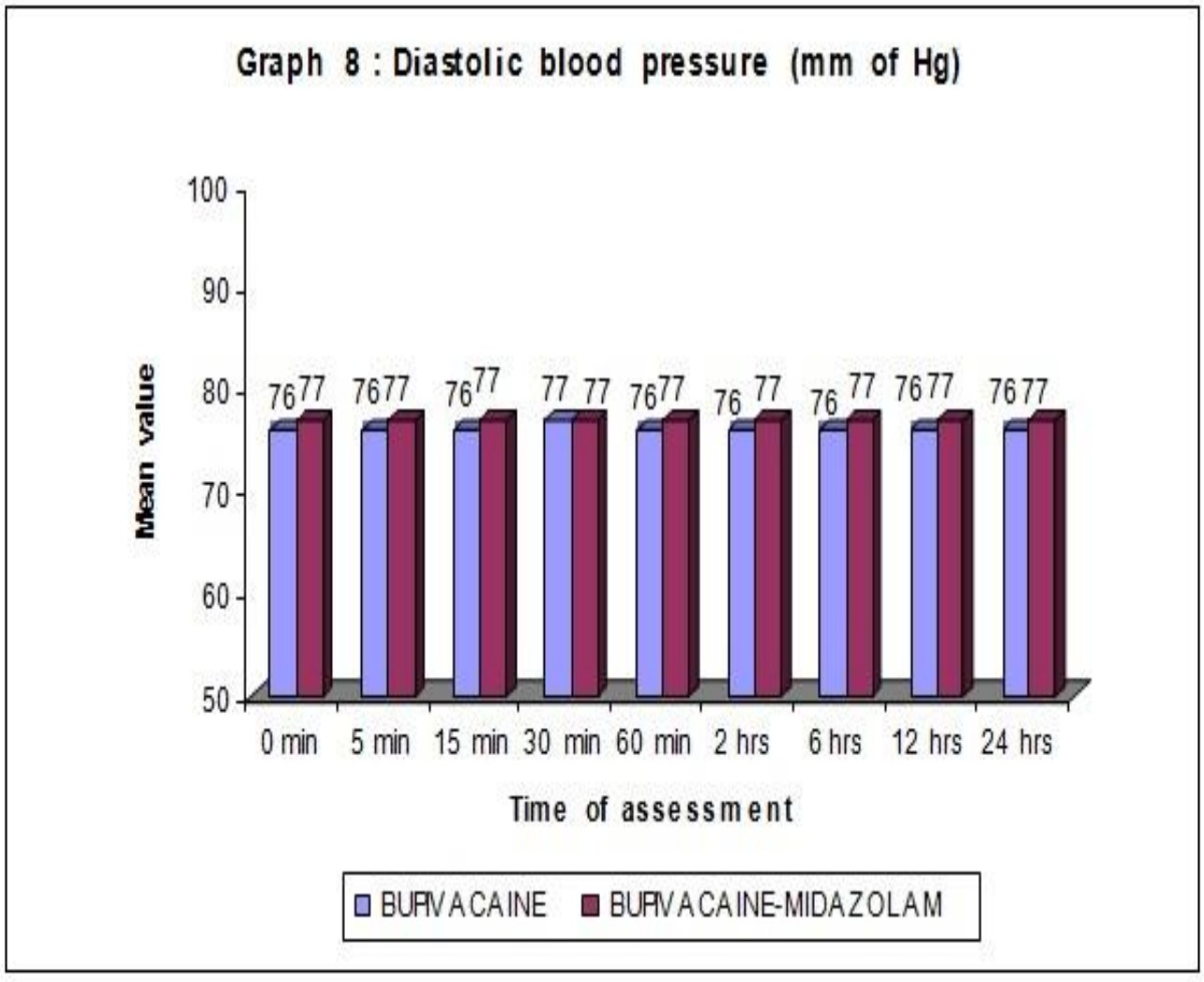


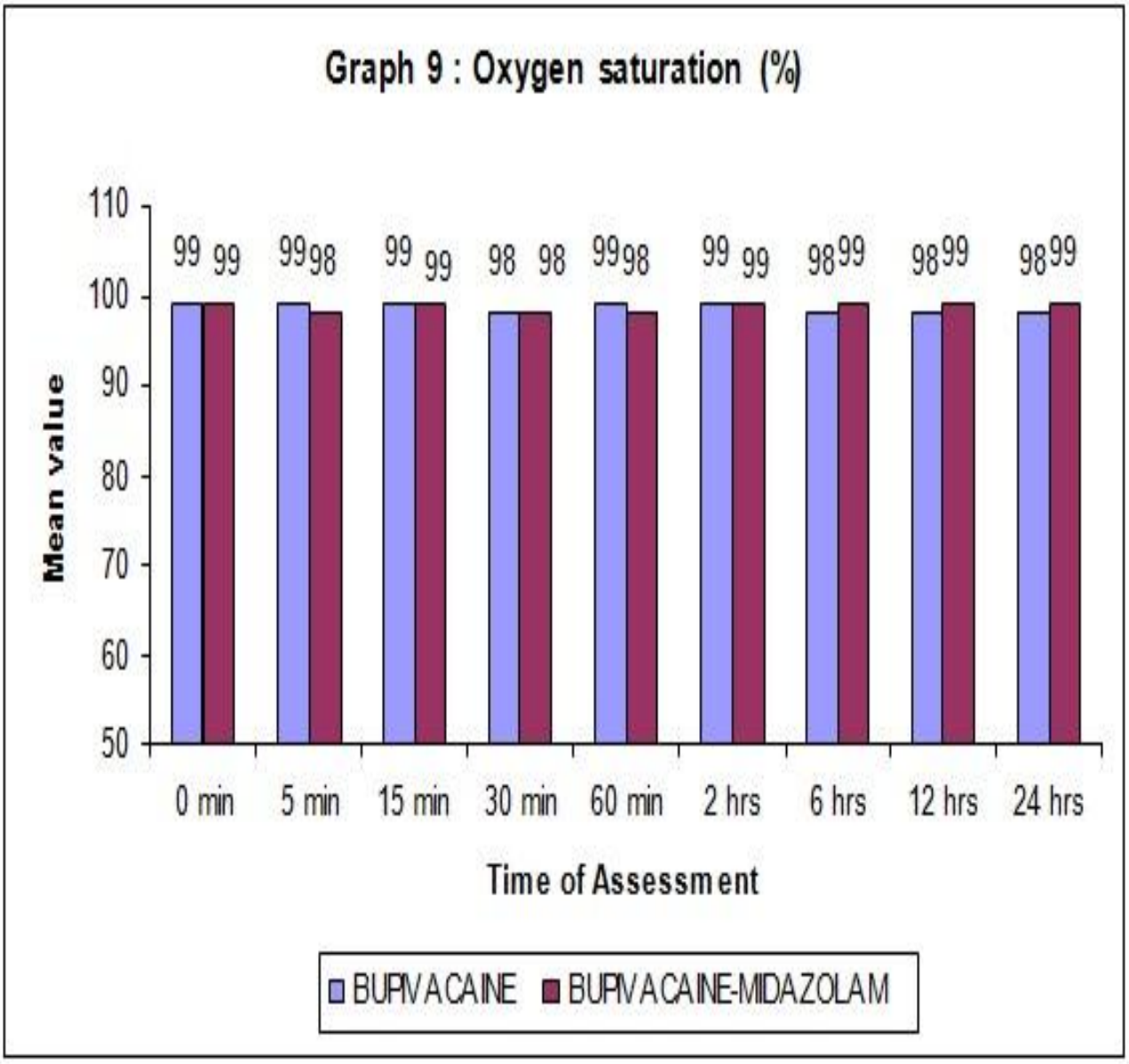
Table 11 : Comparison of Oxygen saturation (%) of Group B and Group BM

Time of Assessment	Mean+/- SD		t* Value	p Value	Significance
	Bupivacaine	Bupivacaine -Midazolam			
0 min	99 ± 0.56	99 ± 0.49	0.01	0.99	NS
5 min	99 ± 0.47	98 ± 0.50	1.8	0.12	NS
15 min	99 ± 0.49	99 ± 0.50	0.39	0.75	NS
30 min	98 ± 0.54	98 ± 0.50	2.09	0.10	NS
60 min	99 ± 0.50	98 ± 0.50	0.19	0.88	NS
2 hrs	99 ± 0.48	99 ± 0.47	0.20	0.85	NS
6 hrs	99 ± 0.49	99 ± 0.47	2.45	0.09	NS
12 hrs	99 ± 0.57	99 ± 0.46	2.09	0.05	NS
24 hrs	99 ± 0.48	99 ± 0.46	3.58	0.05	NS

* Student's unpaired t test

NS = Not Significant (p value >0.05)

As shown in Table 11, in group B, the mean O_2 saturation ranged from 98 ± 0.5% to 99 ± 0.57%. In group BM, the mean O_2 saturation ranged from 98 ± 0.5%. The statistical analysis by students unpaired 't' test showed that there was no significant difference in O_2 saturation between the two groups ($p > 0.05$).



Discussion

DISCUSSION

Brachial plexus block provides postoperative analgesia of short duration[1], even when a long-acting local anaesthetic like Bupivacaine is used alone. Various adjuvant drugs like Neostigmine[1] ,Opioids[2], Hyaluronidase[3]and Clonidine[4] have been evaluated in conjunction with local anaesthetics to prolong the period of analgesia , but they were found to be either ineffective or to produce an unacceptably high incidence of adverse effects.[4]

This was a prospective , randomized single blinded study carried out at Thanjavur Medical College Hospital, Thanjavur.100 ASA 1 and ASA II patients undergoing elective upper limb surgeries were included in the study. Patients were divided into 2 groups of 50 each . (Group B and Group BM.)Group B received supraclavicular brachial plexus block with 30 ml of 0.375% plain bupivacaine . Group BM received supraclavicular Brachial plexus block with 30 ml of 0.375% bupivacaine with preservative free midazolam 2.5mg. Parameters observed included onset time of sensory block , onset time of motor block , duration of sensory block , duration of motor block , duration of analgesia,number of rescue analgesics needed in the 24 hours post-operative period,haemodynamic changes and sedation score

Patient characteristics across the groups

The patients in our study groups did not vary much with respect to age . The p value was 0.83 for age-wise distribution among the groups (p >0.05),and hence not significant. The mean age group for bupivacaine group in our study was 33.4±10.81 and in bupivacaine-midazolam group was 32.9±12.32.

Nasreen et al [38] also found that there was no significant difference between the age groups.The mean age for bupivacaine group was 32.5±2.47 while in bupivacaine-midazolam was 33.1±1.46 .The p value was 0.3010 for age-wise distribution among the groups (p >0.05).

In another study by Koj Jarbo et al [28] ,the mean age for group B(bupivacaine) is 33.2±9.29 and the mean age group for BM(bupivacaine-midazolam) was 33.65±9.34, the p value for age-wise distribution was >0.05,hence not significant.This was in concordance with our study in which mean age did not vary much among the groups.

Changes in the perioperative cardiovascular parameters

There were no significant differences between the study groups with respect to pattern of changes in pulse rate, systolic blood pressure, diastolic blood pressure perioperatively .The pulse rate was recorded at 0 min,5 min,15

min, 30 min ,60 min,2 hours, 6 hours,12 hours and 24 hours.The p values measured during these intervals were found to be not significant(p>0.05).The diastolic and systolic blood pressure was recorded 0 min,5 min,15 min, 30 min, 60 min,2 hours, 6 hours,12 hours and 24 hours.The p values recorded during the intervals were found to be not significant.(p>0.05).Likewise,oxygen saturation(%) was also recorded during the same time intervals,which was not significant(p value >0.05)

Koj Jarbo et al[28] in their study, concluded that heart rate,systolic blood pressure,diastolic blood pressure,mean arterial blood pressure,oxygen saturation were comparable between the study groups(plain bupivacaine and bupivacaine-midazolam) and did not change significantly in the intra or postoperative period.

Nasreen et al[38] in their study concluded that the hemodynamic variables were comparable between the age groups and did not change significantly in the intraoperative and post operative period.

In a study conducted by Shaikh et al[34], they found no statistically significant hemodynamic changes when midazolam was added to bupivacaine in supraclavicular brachial plexus block (p>0.05).In another study conducted by Batra et al,[7]they found no statistical difference in hemodynamic parameters

when preservative free midazolam was added to intrathecal bupivacaine($p>0.05$) .

These findings correlates with our study in which haemodynamic variables were comparable between the study groups.

Onset time of Sensory block

In our study, we found out that the onset of sensory blockade was significantly faster in patients who received a combination of midazolam and bupivacaine. The mean value for the onset of sensory block for group BM was 11.26 ± 1.5 min; while in group B was 19.08 ± 1.7 min.The p value was found to be 0.0007 ,which was found to be statistically significant ($p<0.05$).

These values were in conjunction with that of the study conducted by Koj Jarbo et al [28] in which they found out that the mean value for the onset of sensory block was significantly faster in group BM (12±2.9 mins) when compared to group B (20±3.8),($p <0.05$),which was statistically significant. Hence, the authors concluded that preservative free midazolam 2.5mg added to bupivacaine has an advantage of early onset of sensory blockade when compared to plain bupivacaine for supraclavicular brachial plexus block. This could be due to the local anaesthetic property of Midazolam and its synergistic action with that of local anaesthetics.[14]

In another study by Nasreen Laiq et al [38], the onset of sensory block appeared earlier in group B(bupivacaine –midazolam group) than in group A(plain bupivacaine group) . In group B, the mean value for onset of sensory block occurred in 14 ± 3.1 minutes compared to 22 ± 3.5 minutes in group A.The p value was found out to be less than 0.001,hence statistically significant.

These values were in concordance with our study in which mean onset time of sensory block was faster in bupivacaine-preservative free midazolam group compared to plain bupivacaine group.

In a study conducted by Shaikh et al [34] ,they found no statistical difference in the onset of sensory block when midazolam was added to bupivacaine.The mean value for onset of sensory block in plain bupivacaine group was 8.36$\underline{+}$3.58mins while in bupivacaine-midazolam was 8.52$\underline{+}$4.18.They found the p value to be more than 0.05,hence statistically not significant.They concluded that the onset of sensory blockade was same for both the groups.

This was in contrast with our study that the onset of sensory blockade was earlier in bupivacaine-midazolam mixture.

Onset of Motor Block

In our study, we found out that the onset of motor blockade was significantly faster in patients who received a combination of preservative free midazolam and bupivacaine. Onset of motor block for group BM was 9.56 ± 1.32 min and in group B was 15.30 ± 2.09 min, which was statistically significant($p = 0.0009$).

These values were in conjunction with that of the study of Koj Jarbo et al [28] in which they found out that the onset of motor block was significantly faster in group BM (9.2 ± 2.38 mins) when compared to group B (17.1±3.83),which was statistically significant($p < 0.05$).

Nasreen Laiq et al [38] also found that the onset of motor block appeared earlier in group B(bupivacaine –midazolam group) than in group A(plain bupivacaine group) .In group B, the onset of motor block occurred in 10.5± 2.40 minutes compared to 18.5 ± 3.50 minutes in group A.The p value was found to be less than 0.001,hence statistically significant..

Shaikh et al[34] conducted a study in which they found that the onset of motor blockade was 9.96±5.69 mins in plain bupivacaine group compared to 7.92 ± 5.68 mins. The p value was found to be more than 0.05, hence statistically not significant.

This was in contrast with our study in which there is significant difference between the onset of motor blockade among the study groups.

The onset of motor block was found to be faster than the onset of

sensory block in both groups. Winnie et al.[11], observed this also, and attributed this to the somatotrophic arrangement of fibres in a nerve bundle at the level of the trunks in which motor fibres are located more peripherally than sensory fibres. Hence, a local anaesthetic injected perineurally will begin to block motor fibres before it arrives at the centrally located sensory fibres.

Midazolam a water soluble benzodiazepine is known to produce antinociception and to enhance the effect of local anaesthetic when administered intrathecally and epidurally. Midazolam produces this effect by its action GABA receptors. GABA receptors are also found in peripheral nerves[5]

Duration of Sensory block

In our study the mean duration of sensory block in group BM was 13.81 ± 1.23 hours and in group B was 5.84 ± 0.49 hours.The mean duration of sensory block was significantly higher (P = 0.0003) in group BM (bupivacaine-midazolam) than in group B(bupivacaine).

These values were comparable with the study conducted by Koj Jarbo et al [28],Nasreen et al[38] and Shaikh et al[34].

In the study conducted by Koj Jarbo et al [28]the duration of sensory block was 7±4.32 hours for BM group(bupivacaine-midazolam) compared to group B which was 5.95 ±1.4 hours.The

p value was found to be less than 0.05,hence statistically significant. They concluded that midazolam(0.05mg/kg) added to bupivacaine (0.5%) hastened the onset of sensory and motor block, and prolonged sensory blockade in brachial plexus block,without producing any adverse effects.

Nasreen et al[38] conducted a study in which the duration of sensory blockade was 9.30±4.30 hours compared to 6.20±1.80 hours plain bupivacaine.The p value was found out to be 0.002,which was significant($p<0.05$).

Shaikh et al[34] conducted a study in which they found that the mean duration of sensory blockade was 502.24±52.68 mins in plain bupivacaine group compared to 805.04 ± 175.75 mins. The p value was found to be less than 0.001, hence statistically significant.They concluded that addition of midazolam to bupivacaine in supraclavicular block prolonged sensory blockade without any adverse effects.

Duration of Motor Blockade

In our study, the mean duration of motor block in group BM was 5.25 ± 0.45 hours and the group B was 5.13 ± 0.45 hours.This result was not found to be statistically significant($p = 0.12$)These values were comparable with the study conducted by Koj Jarbo et al[28] in which they found out that the

mean duration of motor blockade in group BM was 5.65 ± 3.32 hours while in group B was 5.1± 1.14 hours.This difference was statistiscally not significant(p value more than 0.05).

Nasreen Laiq[38] also found in their study that the duration of motor blockade was significantly prolonged in Group bupivacaine-midazolam(7.65±3.2 hours) when compared to Group bupivacaine (5.20±2.10 hours)alone,which was found to be statiscally significant(p=0.0024).

In another study conducted by Shaikh et al[34],there was statistically significant prolongation of motor block in group BM than in group B.The duration of motor blockade was 450.48±48 mins in group B when compared to group BM which was 608.96±157.75 mins and this difference was statistically significant(p<0.001).

Our results showed that sensory block tended to last longer as compared to motor block which agrees with the observation by de Jong et al[42]. These authors explained that large fibres require a higher concentration of local anaesthetic than small fibres. The minimal effective concentration of local anaesthetic for large (motor) fibres is greater than for small (sensory) fibres. Thus, motor function return before pain perception and duration of motor block is shorter than the sensory block[18]. However in our study duration of motor blocks were not different between the groups.

Duration of Analgesia

The mean time from onset of block to request of analgesics was taken as total duration of analgesia . The duration of analgesia was 13.81±1.23 hours with bupivacaine-midazolam group (Group BM) and 5.84±.0.49 hours with bupivacaine group (Group B) in our study .

The duration of analgesia was longer in bupivaine-midazolam group compared with bupivacaine group ,which was statistically significant.(p=0.0003),[p value less than 0.05].

Our study correlates with the study conducted by Gulec et al[32],Shaikh et al[34],Nasreen et al[38] , Nishiyama et al[23] ,Batra et al and Trivedi et al[43]. Gulec et al.[32], found that caudal injection of plain bupivacaine and midazolam combination provides a prolonged postoperative analgesia when compared to bupivacaine – morphine combination. The durations of analgesia were 21.15± 1.2 hrs in bupivacaine-midazolam group,14.50± 1.6 hrs in bupivacaine-morphine group and 8.15± 1.3 hrs in bupivacaine group.The difference between plain bupivacaine and bupivacaine-midazolam group was statistically significant(P<0.001),bupivacaine-midazolam and bupivacaine-morphine group was also significant(P<0.01).

This study supports the fact that midazolam prolongs post-operative analgesia when used along with bupivacaine.

Shaikh et al[34] conducted a study in which they found that the mean duration of analgeisa was 502.24±52.68 mins in plain bupivacaine group compared to 805.04 ± 175.75 mins. The p value was found to be less than 0.001, hence statistically significant.They concluded that addition of midazolam to bupivacaine in supraclavicular block prolonged post-operative analgesic effects without any adverse effects.

In another study by Nasreen et al[38] ,they found out that lower pain scores were observed in group B(bupivacaine-midazolam group)compared to group A(plain bupivacaine) for 24 hours postoperatively ($p < 0.001$).The duration of analgesia was 9.30± 4.30 hours compared to 6.20±1.80 hours plain bupivacaine.The p value was found out to be 0.002,which was statistically significant($p<0.05$).

Nishiyama et al.,[23] in their study, added midazolam to a continuous epidural infusion of Bupivacaine and they observed improved analgesia with bupivacaine-midazolam mixture . Time to first analgesic administration were longer ($P < 0.001$) in the bupivacaine-midazolam group than in the other

groups.This fact supports that midazolam prolongs analgesic effects of bupivacaine.

Batra et al.[20] used bupivacaine with midazolam intrathecally and found a significantly prolonged analgesia when compared to bupivacaine alone. A significantly higher Visual Analogue score ($P < 0.05$) was seen in group B (bupivacaine alone) when compared to group BM (bupivacaine-midazolam) group.

Trivedi V et al[43] conducted a study to compare the effects of midazolam and clonidine added to bupivacaine and they found out that clonidine provides better post operative analgesia when compared with midazolam.

Number of Rescue Analgesics used

In our study, in group BM, 74% patients required only 1 rescue analgesic dosage and 26% of patients required 2 rescue analgesic doses in post-op 24 hours. In group B 76% of patients required 2 and 24% of patients required 3 rescue analgesic doses in post-op 24 hours. This difference in number of rescue analgesic doses required by patient of both groups was statistically highly significant by chi-square test ($\chi^2 = 61.25$, $p< 0.001$).The number of patients who required rescue analgesia and the mean number of supplemental analgesia were less in bupivacaine-midazolam group

Our study correlates with the study by Jarbo et al[28] in which they found out the number of rescue analgesic doses was higher (n=58) in plain bupivacaine group when compared to bupivacaine-midazolam group(n=8),which was significant($p<0.05$).

In another study by Nasreen et al[38] , almost all patients in plain bupivacaine group required rescue analgesia, while only 5 patients (20%) of midazolam-bupivacaine group required rescue analgesics in order to maintain analgesia in the first 24 hours($p <0.001$),which was found to be significant.These values were in concordance with our study.

Similar observation was made in the above mentioned study by Koj Jarbo et al [28].

These values were in concordance with Naguib et al [29] in which they found out that the time of first analgesic administration were longer ($P < 0.001$) in bupivacaine-midazolam group when compared to plain bupivacaine group. Further, the bupivacaine-midazolam group received fewer ($P < 0.05$) doses of rescue analgesics than plain bupivacaine group.They concluded that caudal injection of bupivacaine-midazolam reduced the requirement of rescue analgesics.

In another study conducted by A.Kharbasfrushan et al[40], The average time until the first dose of additional analgesic was 142.18±55.19 min in the

BNS(bupivacaine-normal saline) vs 178.06±77.33 min in the BM(bupivacaine-midazolam) group(p value <0.05). They concluded that combination of bupivacaine (10 mg) plus intrathecal midazolam (2 mg) was an effective anesthetic technique to provide improvement in pain.

The prolonged analgesia in Group BM could be due to the action of Midazolam on GABA-A receptors[19] present in the brachial plexus and thus producing antinociception

Sedation Score

We studied Midazolam at a dose of 2.5 mg, as others have used the same dosage in central neuraxial block without any significant adverse effects. In our study, sedation scores were higher in patients in Group BM compared to Group B, 15 minutes to 60 minutes from the time of injection of drug.

In our study, in group B all patients were awake and alert and had sedation score of 1. In group BM, sedation corresponding to score 2 was observed in some patients between 15 minutes from time of injection to 60 minutes. 20% of patients at 15 minutes, 32% of patients at 30 minutes and 26% of patients at 60 minutes had sedation score of 2. None of the patients had sedation score of 3 and above during the study period. Statistical analysis of sedation score by chi-square test showed that the difference in

sedation score was significant ($p < 0.05$) during 15, 30 and 60 minutes.

Our study correlates with the studies conducted by Jarbo et al[28], Shaikh et al[34] ,Nasreen et al[38] ,Sibel Baris et al[39], Kharbasfrushan et al[40]

Similar observations were made in the study by Shaikh et al[34].In their study,group B patients were all awake(score 1)while group BM patients had a sedation score of 2 during the first 60 mins.

In another study by Jarbo et al[28],they found out that 11 patients had a sedation score of 2 between 10 minutes to 20 minutes from the time of injection.

This could be due to partial vascular uptake of Midazolam, and its transport to the central nervous system where it acts and produces sedation. Adding midazolam not only provides prolonged post-operative analgesia but also sedation as in a study described by Nishiyama et al[24]

In another study conducted by Nasreen et al[38], perioperatively sedation scores were higher in group B compared to group A ($p < 0.001$) as patients in group A were all awake (score 1) throughout the intraoperative period while in

group B, 6 patients at 10 minutes, 10 patients at 20 minutes and 15 patients at 30 minutes were sedated and responded to verbal stimulation (score 2). The highest sedation score was 2 in group B and no patient had sedation score of 3 or more that required assistance for airway maintenance.This was in accordance with our study.

In a study conducted by A.Kharbasfrushan et al[40] sedation was present in the group that received bupivacaine plus intrathecal midazolam compared with those who received intrathecal bupivacaine plus normal saline when given ($p<0.05$),hence statistically significant.

In another study conducted by Sibel Baris et al[39], sedation score was higher in the BM(bupivacaine-midazolam) group at 60 and 90 minutes postoperatively than the other groups(plain bupivacaine and bupivacaine-fentanyl).The result was statistically significant(p value <0.05)

The limited duration of sedation could be explained by the fact that midazolam is highly lipophilic and diffuses faster into the blood vessels, by its rapid clearance (6-11 $mL.kg^{-1}.min^{-1}$) and short half-life (1.7-2.6 hr)[44] .Though mean sedation score in group BM was higher as compared to group B ($P < 0.05$), we did not observe clinically significant sedation in patients in group BM. No patient experienced airway compromise or required

airway assistance. This mild sedation was actually desirable during that period.This values are comparable with the Shaikh et al[37] and with that of Koj Jarbo et al[28]

In a study, Gupta et al[41], the median effective volume [95% confidence interval (CI)] for 0.25%, 0.375%, and 0.5% bupivacaine for supraclavicular block was 26.8 (18.6-38.4), 18.1 (12.1-26.0), and 12.0 (8.4-17.3) ml, respectively. The median effective dose(ED_{50}) (95% CI) for 0.25%, 0.375%, and 0.5% bupivacaine was 66.9 (46.6-96.0), 68.0 (47.4-97.6), and 60.1 (41.8-86.3) mg, respectively. The difference in the ED_{50} dose between the three concentrations was not statistically significant. This study demonstrated that the ED_{50} dose of bupivacaine for supraclavicular block was not dependent on the concentration.In our study, 0.375% of 30 ml bupivacaine was used unlike that of the study of Koj Jarbo et al[28] ,Shaikh et al [34] and Nasreen et al[38].But the the study given above proved the fact that success rate of block did not depend upon the concentration.

Mamoun al Basheer et al [45] also used 0.375% of 30 ml of bupivacaine for brachial plexus block in 288 patients undergoing vascular access surgeries for renal dialysis. All patients had an adequate block with no conversions to general anesthesia or cancellation of the procedure. A successful block was achieved in 232 (80.6%) patients while a partially successful block was

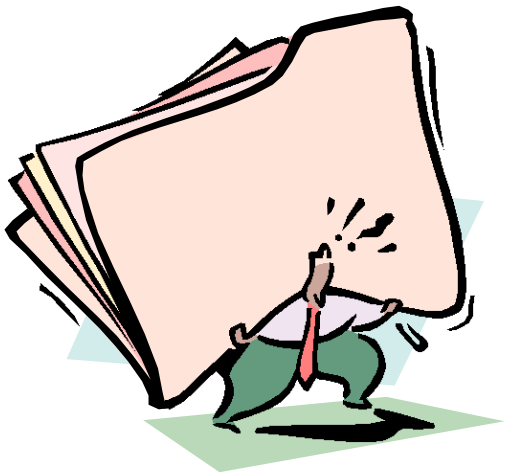
achieved in 56 (19.4%) patients. The median time for onset of the block was 10 (5-20) minutes for motor block and 15 (10-35) minutes for sensory block. The mean duration of the block was 5.6 (2.2-48.0) hours. Prolonged blocks beyond 24 hours occurred in 5 patients (48 hours in 1 patient, 36 hours in 1 patient, and 24 hours in 3 patients). No clinically detectable pneumothorax or drug toxicity occurred. No peri-operative mortality was reported during the study period.In this study, they have used 0.375% of bupivacaine and they found out equally good success rate when compared to 0.5% bupivacaine.This result was in concordance with our study.

Walter Pinto et al[46] also used 0.375% bupivacaine for cervical plexus block for carotid endarterectomy. The objective of this study was to compare the analgesic effects of 150 mcgs clonidine added with bupivacaine to those of bupivacaine in cervical plexus block.They conducted the study in 30 patients undergoing carotid endarterectomy. They concluded that addition of 150 μg of clonidine and bupivacaine in cervical plexus block for carotid endarterectomy did not significantly improve the analgesic effects evaluated by pain score, time until the first rescue analgesics. This study also supported the fact that 0.375% of bupivacaine provided equally good success rate when compared to 0.5% bupivacaine.This result correlated with that of our study.

Jean J et al[47] compared the effects of clonidine and epinephrine added 0.25% of 40 ml to 50 ml of bupivacaine in supraclavicular brachial plexus

block. In this study,60 ASA I and II patients were randomly allocated into 2 groups of 30 each.Group I receiving clonidine 150 mcgs and group II receiving epinephrine 200 mcgs.They concluded that block produced by clonidine was superior when compared to block produced by epinephrine($p<0.001$).This study also demonstrated the fact that mean effective dose of bupivacaine needed for supraclavicular brachial plexus block did not depend upon the concentration.

In conclusion, "preservative free midazolam 2.5 mg when added to 30mL of Inj. bupivacaine 0.375% for supraclavicular brachial plexus block, speeds the onset of sensory and motor blocks ($P < 0.05$). This combination produced prolonged analgesia and reduced requirements for rescue analgesics.



Summary

SUMMARY

We conducted a prospective randomised single blinded study "A clinical comparison between bupivacaine- midazolam(preservative free.) combination and bupivacaine (plain) in brachial plexus block by supraclavicular approach" was conducted in 100 patients ASA grade I and II admitted to Thanjavur Medical College hospital,Thanjavur ,for upper limb surgeries .Patients of both sexes, ranging between 15-55 years of age,were included.

Our aim was to compare the efficacy of adding 2.5 mg of midazolam(preservative free) to 0.375% Inj.bupivacaine with plain Inj.bupivacaine(0.375%) for onset and duration of motor and sensory blockade,haemodynamic stability,sedation score,requirements of rescue analgesics in the immediate 24 hours post-operative period.

The patients were randomly divided into 2 groups :

Group BM – Received 30 ml of 0.375% Inj.bupivacaine + 2.5 mg of Inj.midazolam(preservative free)

Group B – Received 30 ml of 0.375% Inj. bupivacaine only.

The following parameters were recorded and compared.

1) Onset of sensory and motor block
2) Duration of sensory and motor block
3) Number of rescue analgesics in the immediate 24 hours post-operatively

4) Sedation score

5) Changes in heart rate, systolic and diastolic blood pressure and O_2 saturation were noted in both groups.

Data collected were analysed with the help of computer using Epidemiological Information package (2008). Using this software range, frequencies, percentages, means, standard deviations, chi square and 'p' values were calculated. Student's 't' test was used to text the significance of difference between quantitative variables and Yate's test for qualitative variables. A 'p' value less than 0.05 is taken to denote significant result.

We found out that:

1. Addition of midazolam to local anesthetic solution (Bupivacaine) shows early onset of sensory blockade compared to Bupivacaine alone.
2. Addition of midazolam to Bupivacaine shows early onset of motor blockade compared to Bupivacaine alone.
3. Addition of midazolam to local anaesthetic solution significantly prolongs the duration of analgesia compared to Bupivacaine alone.
4. Addition of midazolam to Bupivacaine increases the duration of sensory blockade compared to Bupivacaine alone.
5. Addition of midazolam to Bupivacaine does not prolong motor blockade when compared to Bupivacaine alone.

6. Number of rescue analgesics used were less in Bupivacaine-Midazolam group when compared to Bupivacaine(alone) group
7. In midazolam group intra operative sedation is well observed without compromising respiratory function or any need of airway assistance.
8. Both groups were comparable with regard to pulse rate, systolic blood pressure, diastolic blood pressure and O_2 saturation

Conclusion

CONCLUSION

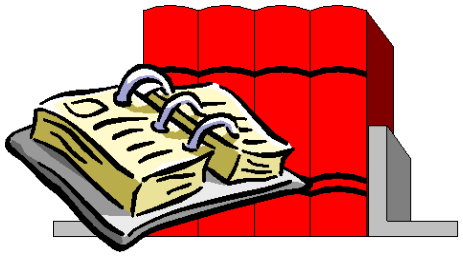
From our study, we conclude that, the addition of Midazolam (2.5 mg) as an adjuvant to bupivacaine (0.375%) when compared to plain bupivacaine(0.375%) resulted in :

i) Rapid onset of sensory block and motor block.

ii) Prolonged duration of sensory block.

iii) Reduced number of rescue analgesics in the post-operative period of 24 hours.

iv) Patients were hemodynamically stable.



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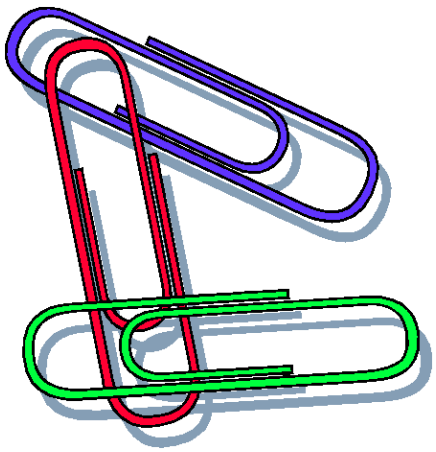

Annexures

ANENXURE I

PROFORMA

Name : I.P. No. :

Age : Hospital :

Sex : Date :

PREOPERATIVE OBSERVATIONS :

General physical examination :

Pulse rate :----------bpm

B.P. :----------mm of Hg

R.R :----------cycles/min

Systemic examination :

C.V.S :

R.S. :

Others :

Investigations :

Hb% : F.B.S. / R.B.S. : ECG :

Blood urea : S.Creat : Urine :

Preoperative diagnosis :

Proposed surgery :

Premedication : Inj. Ranitidine and inj. Ondansetron

ASA grade :

Anaesthetic technique : Supraclavicular approach to brachial plexus block

STUDY PROTOCOL :

30ml of 0.375% bupivacaine with midazolam (0.05 mg/kg) or 30ml of 0.375% bupivacaine alone.

Time of injection :

Time of onset of motor block : _____ min

Time to onset of sensory block : _____ min

MONITORING :

	Pulse rate	**SPB mm of Hg**	**DBP mm of Hg**	**SpO_2 %**	**Sedation score**
0 min					
5 min					
15 min					
30 min					
60 min					
2 hrs					
6 hrs					
12 hrs					
24 hrs					

Duration of motor blockade : _____ hrs.

Duration of sensory blockade : _____ hrs.

No. of rescue analgesics in post-op 24 hrs. _____ hrs

ANNEXURE -II

MASTER CHART

MASTER CHART

BUPIVACAINE GROUP

Sl. No.	Patient Name	IP. No.	Age (yrs)	Onset of Block		Duration of block		No. of RA in 24 hours post-op	Sedation score									Pulse Rate (beats/min)									Systolic BP (mm of Hg)									Diastolic BP (mmg Hg)									O2 Saturation (%)								
				Sensory (min)	Motor (min)	Sensory (min)	Motor (min)		0 min	5 min	15 min	30 min	60 min	2 hrs	6 hrs	12 hrs	24 hrs	0 min	5 min	15 min	30 min	60 min	2 hrs	6 hrs	12 hrs	24 hrs	0 min	5 min	15 min	30 min	60 min	2 hrs	6 hrs	12 hrs	24 hrs	0 min	5 min	15 min	30 min	60 min	2 hrs	6 hrs	12 hrs	24 hrs	0 min	5 min	15 min	30 min	60 min	2 hrs	6 hrs	12 hrs	24 hrs
1	Ranjithkumar	26542	21	19	16	5.4	4.6	3	1	1	1	1	1	1	1	1	1	74	76	75	74	72	74	74	73	75	110	110	110	108	110	108	112	110	110	71	72	71	70	71	72	72	70	71	99	99	98	99	98	99	99	99	98
2	Valarmathy	26192	48	20	14	5.8	4.8	2	1	1	1	1	1	1	1	1	1	78	78	79	77	72	77	76	77	77	122	120	122	124	120	120	120	122	120	81	80	81	82	81	80	82	81	82	99	99	98	98	99	99	99	99	99
3	Rajesh	26802	28	18	16	6.7	5.8	2	1	1	1	1	1	1	1	1	1	88	86	87	87	87	87	88	86	88	104	106	104	104	106	104	102	104	104	68	69	68	70	68	70	71	69	70	99	99	98	98	98	98	99	99	99
4	Muthusamy	31672	53	21	18	6.1	5.7	2	1	1	1	1	1	1	1	1	1	81	80	80	80	79	81	81	80	80	112	112	112	112	114	110	110	110	110	72	71	73	74	71	74	71	71	71	99	99	98	97	98	98	99	99	99
5	Sekar	36002	34	17	12	5.9	4.9	2	1	1	1	1	1	1	1	1	1	69	70	69	69	70	71	70	70	71	120	120	120	120	120	120	120	120	120	83	81	82	81	81	81	81	82	83	99	99	98	99	98	98	99	98	99
6	Vijendran	37773	37	19	17	5.3	4.8	3	1	1	1	1	1	1	1	1	1	84	85	84	83	84	84	85	86	84	108	108	110	110	108	108	110	108	106	68	69	70	71	71	71	69	70	71	98	99	99	99	99	99	99	98	99
7	Nethravathi	37786	24	22	18	6.6	5.4	2	1	1	1	1	1	1	1	1	1	75	76	75	75	76	75	74	75	76	126	124	124	126	126	126	126	124	124	84	85	83	83	84	85	83	83	83	99	99	99	99	99	99	99	99	99
8	Uma	37812	22	16	12	5.8	5.0	2	1	1	1	1	1	1	1	1	1	76	75	74	75	75	76	77	77	76	134	134	134	134	132	132	132	134	134	88	87	87	88	85	90	91	83	84	98	99	99	98	98	99	99	98	98
9	Revathi	37839	38	19	14	6.5	5.3	2	1	1	1	1	1	1	1	1	1	80	82	80	79	80	79	81	80	82	102	102	102	102	104	102	104	104	102	69	70	71	71	71	71	71	71	70	98	99	98	98	98	99	99	98	99
10	Manjunath	37861	24	17	13	5.2	4.8	3	1	1	1	1	1	1	1	1	1	68	69	67	66	67	67	68	69	68	106	106	108	108	108	108	108	108	108	70	70	70	70	70	72	71	70	69	98	99	99	99	98	98	98	98	99
11	Chestasamy	38111	38	18	15	6.3	5.3	2	1	1	1	1	1	1	1	1	1	71	70	70	69	70	70	71	72	71	120	120	120	118	118	120	120	118	120	85	84	84	85	82	80	81	82	83	98	99	99	99	98	98	99	99	98
12	Yashodha	38162	35	20	18	6.0	5.4	2	1	1	1	1	1	1	1	1	1	79	80	81	79	79	80	80	79	81	122	122	122	122	120	120	120	122	122	85	84	73	83	82	81	81	80	79	99	99	99	99	98	98	98	99	99
13	Suvarna	38200	29	23	19	4.8	3.8	3	1	1	1	1	1	1	1	1	1	79	80	79	81	81	80	82	80	80	108	110	110	108	108	106	108	110	108	69	70	71	72	73	70	71	72	70	99	99	99	98	98	99	99	99	99
14	Lalitha	38281	21	20	18	6.1	5.2	2	1	1	1	1	1	1	1	1	1	72	72	73	72	75	73	74	72	72	130	130	130	130	130	128	128	128	128	81	80	80	80	80	80	79	78	80	99	99	99	98	99	99	98	99	99
15	Suresh	38331	18	21	19	5.7	4.9	2	1	1	1	1	1	1	1	1	1	81	82	82	81	83	82	82	81	83	128	126	126	128	126	124	126	126	126	82	81	80	80	78	79	80	81	80	99	99	99	98	98	98	98	99	99
16	Raja	38333	45	19	13	4.6	3.9	3	1	1	1	1	1	1	1	1	1	69	70	59	69	71	70	69	70	71	106	106	106	106	104	104	104	106	106	66	55	66	66	68	67	66	65	66	99	99	99	98	99	99	98	98	98
17	Swamy	38413	28	18	15	6.6	5.2	2	1	1	1	1	1	1	1	1	1	73	73	73	74	75	73	72	83	71	130	128	128	128	130	130	130	130	128	76	74	75	75	75	73	72	72	72	99	99	99	98	99	99	98	99	99
18	Adaikalam	38469	47	20	13	5.7	5.4	2	1	1	1	1	1	1	1	1	1	85	84	84	83	84	85	86	82	83	102	102	102	102	104	102	102	100	102	74	75	74	74	74	74	76	72	74	99	98	99	98	99	99	98	99	99
19	Surya	505632	16	21	17	6.2	5.6	2	1	1	1	1	1	1	1	1	1	68	65	70	70	70	71	68	69	70	116	118	118	118	118	115	116	116	116	72	70	71	70	71	72	72	73	72	99	98	99	97	99	98	98	99	99
20	Ammulu	506181	51	16	12	6.4	5.8	2	1	1	1	1	1	1	1	1	1	72	73	74	72	71	72	72	73	72	122	122	120	120	120	122	120	120	120	80	79	79	80	81	82	83	81	82	99	98	99	99	99	98	98	99	99
21	Jayanth	509372	54	20	15	6.1	5.2	2	1	1	1	1	1	1	1	1	1	82	80	79	80	81	82	82	81	80	114	113	116	114	114	112	114	114	114	64	66	66	66	67	65	66	65	66	99	98	99	98	99	98	98	99	98
22	Venkatesh	509929	31	21	18	4.7	4.9	3	1	1	1	1	1	1	1	1	1	78	77	78	79	80	81	80	78	79	126	126	126	126	128	126	124	126	126	86	84	85	84	85	86	86	87	86	98	99	99	99	98	98	98	99	99
23	Gomathi	516283	38	19	16	6.5	5.8	2	1	1	1	1	1	1	1	1	1	64	65	64	66	65	65	64	66	86	134	132	132	134	130	132	132	132	132	88	86	85	86	86	89	89	89	87	97	99	99	98	98	98	98	99	99
24	Priya	514926	22	17	12	6.1	5.6	2	1	1	1	1	1	1	1	1	1	62	63	62	62	64	63	62	63	62	128	130	128	128	128	130	130	130	130	88	85	85	86	87	87	86	87	87	97	99	98	98	98	98	98	99	98
25	Ganesh raj	521687	37	18	15	4.9	4.8	3	1	1	1	1	1	1	1	1	1	88	87	88	88	89	89	87	88	89	108	108	110	108	108	108	110	110	110	68	69	70	71	71	71	71	71	71	98	99	98	98	98	98	99	99	99

26	Parvathi	50105	38	18	16	5.3	4.8	3	1	1	1	1	1	1	1	1	1	89	90	91	90	89	88	89	88	90	134	130	132	130	132	130	132	132	130	86	86	86	84	84	84	84	86	86	99	98	99	98	99	99	99	99	98
27	Mahmood	50105	51	17	13	5.7	5.0	2	1	1	1	1	1	1	1	1	1	67	66	66	65	67	66	65	67	67	126	126	126	124	120	124	122	124	124	80	82	82	82	80	80	80	80	80	99	99	99	98	99	99	99	99	99
28	Nagraj	45312	22	19	16	6.2	5.7	2	1	1	1	1	1	1	1	1	1	79	80	81	79	80	80	81	74	79	114	114	124	124	116	112	110	110	110	72	74	74	70	70	70	74	74	74	99	99	99	98	98	98	99	99	98
29	Devi	45389	28	21	18	6.0	5.4	2	1	1	1	1	1	1	1	1	1	83	83	82	83	81	83	82	82	82	122	120	120	122	120	122	120	122	120	82	84	84	84	84	84	84	84	84	99	99	99	98	99	99	99	98	99
30	Shankar	45400	33	19	16	5.3	4.9	3	1	1	1	1	1	1	1	1	1	78	77	77	78	78	79	77	77	78	118	116	118	120	116	118	120	116	120	70	72	70	72	70	72	70	72	70	99	99	99	98	99	99	99	98	98
31	Deepa	45562	20	17	13	5.9	4.8	2	1	1	1	1	1	1	1	1	1	74	75	75	74	75	74	76	75	79	116	118	118	118	118	116	120	120	118	68	70	70	70	68	68	68	68	70	99	98	99	98	99	99	99	99	99
32	Pappathi	45712	28	20	17	6.1	5.3	2	1	1	1	1	1	1	1	1	1	86	85	86	87	88	88	86	85	86	102	104	104	104	104	102	104	104	104	66	68	66	66	66	66	66	68	66	99	98	98	98	98	98	98	98	99
33	Iqbal	45846	28	20	14	6.2	5.5	2	1	1	1	1	1	1	1	1	1	72	73	73	72	71	72	73	70	70	130	132	130	132	130	130	130	128	130	88	86	86	88	88	88	88	88	88	99	98	98	99	99	99	99	99	99
34	Kumar	46871	30	18	15	5.9	4.7	2	1	1	1	1	1	1	1	1	1	66	67	67	68	69	68	67	66	66	106	106	106	104	108	108	104	106	106	70	68	68	68	68	68	72	72	72	99	98	98	99	99	99	99	99	99
35	Jayan	54005	48	19	13	5.9	4.9	2	1	1	1	1	1	1	1	1	1	79	80	80	81	81	80	79	78	77	128	130	128	130	128	128	130	130	128	84	82	82	82	82	82	82	82	82	99	99	98	99	99	99	99	99	99
36	Jackson	52105	17	21	16	5.8	4.9	3	1	1	1	1	1	1	1	1	1	87	86	85	87	88	89	86	84	85	130	128	126	126	126	126	126	126	126	86	88	88	88	86	86	88	88	88	99	99	98	99	99	99	99	99	98
37	Anitha	52205	20	20	14	5.2	4.7	3	1	1	1	1	1	1	1	1	1	73	74	70	71	72	73	73	72	70	108	106	108	110	110	110	110	110	110	72	74	74	74	72	74	74	74	74	98	98	98	99	99	99	99	98	99
38	Gunamoorthy	52205	42	23	19	5.9	4.9	2	1	1	1	1	1	1	1	1	1	85	83	82	80	81	83	81	82	80	102	100	100	100	104	104	104	104	104	68	70	70	70	68	68	68	68	68	98	98	98	99	99	99	99	98	99
39	Asif Khan	55205	46	20	18	5.6	5.0	2	1	1	1	1	1	1	1	1	1	70	71	71	71	70	69	72	72	70	122	120	124	124	124	124	124	124	124	88	86	86	88	88	88	88	86	86	98	98	98	98	99	99	99	98	99
40	Raghavendra	50105	40	18	14	6.2	5.6	2	1	1	1	1	1	1	1	1	1	80	79	79	80	78	79	81	80	82	120	118	118	118	122	122	122	122	122	70	68	68	68	68	70	70	70	70	98	98	98	98	98	99	99	98	98
41	Veeramoorthy	62105	50	17	14	6.0	5.2	2	1	1	1	1	1	1	1	1	1	68	67	68	67	68	70	71	69	70	106	104	104	108	108	108	108	108	108	70	70	70	70	70	70	70	70	70	98	98	98	98	98	98	98	99	99
42	Hashim	61105	19	19	15	6.1	5.6	2	1	1	1	1	1	1	1	1	1	77	77	78	78	75	76	75	76	75	102	104	104	102	102	100	100	100	100	68	68	68	68	68	68	68	68	70	99	99	98	98	98	99	99	98	99
43	Pattammal	61105	31	16	12	6.3	5.7	2	1	1	1	1	1	1	1	1	1	86	85	84	85	83	84	83	82	84	108	106	108	106	108	106	108	106	108	74	76	74	74	74	74	74	74	74	99	99	99	98	98	99	99	98	99
44	Pallavi	48136	26	21	17	5.9	4.8	2	1	1	1	1	1	1	1	1	1	82	81	80	80	79	81	80	80	79	130	132	130	132	130	132	132	128	128	88	86	88	86	88	86	88	86	88	98	99	99	99	98	99	98	98	99
45	Shanmugapriya	48318	33	19	14	5.8	4.8	2	1	1	1	1	1	1	1	1	1	72	73	73	73	72	72	71	72	70	112	110	110	110	110	110	110	110	110	74	74	74	74	74	74	74	74	74	99	98	99	99	98	99	98	99	99
46	Ganesh	49112	36	19	15	5.9	5.4	2	1	1	1	1	1	1	1	1	1	74	75	75	76	76	76	74	73	74	112	114	114	114	114	114	114	114	114	72	74	72	72	72	74	74	74	74	99	98	99	98	99	99	98	99	99
47	Rehmattulla	49116	28	17	13	5.1	5.8	3	1	1	1	1	1	1	1	1	1	81	80	79	79	80	79	82	82	82	136	138	138	138	134	134	134	134	134	84	86	86	86	82	72	72	72	72	98	98	99	98	99	99	98	99	99
48	Janardhana	49378	26	18	16	5.9	4.9	2	1	1	1	1	1	1	1	1	1	69	69	70	69	71	71	71	69	70	120	122	122	122	122	122	122	122	122	72	72	72	74	74	72	72	72	72	98	99	99	98	98	99	98	99	99
49	Selvaraj	49431	48	19	15	5.8	4.7	2	1	1	1	1	1	1	1	1	1	79	80	80	80	79	79	81	80	81	128	126	126	126	126	126	126	126	126	78	78	78	80	80	80	76	76	76	99	99	98	98	99	98	98	99	98
50	Shahjahan	611005	43	20	17	6.4	5.6	2	1	1	1	1	1	1	1		1	77	77	76	75	78	77	76	77	79	108	106	110	110	110	110	106	106	106	68	70	68	72	68	72	72	72	72	99	99	98	98	99	99	98	98	98

MASTER CHART

BUPIVACAINE - MIDAZOLAM GROUP

Sl. No.	Patient Name	IP. No.	Age (yrs)	Onset of Block		Duration of block			Sedation score									Pulse Rate									Systolic BP									Diastolic BP									O2 Saturation								
				Sensory (min)	Motor (min)	Sensory (min)	Motor (min)	No. of RA in 24 hours post-op	0 min	5 min	15 min	30 min	60 min	2 hrs	6 hrs	12 hrs	24 hrs	0 min	5 min	15 min	30 min	60 min	2 hrs	6 hrs	12 hrs	24 hrs	0 min	5 min	15 min	30 min	60 min	2 hrs	6 hrs	12 hrs	24 hrs	0 min	5 min	15 min	30 min	60 min	2 hrs	6 hrs	12 hrs	24 hrs	0 min	5 min	15 min	30 min	60 min	2 hrs	6 hrs	12 hrs	24 hrs
1	Anish	26649	26	12	10	13.1	5.7	1	1	1	1	1	1	1	1	1	1	77	74	72	75	77	76	75	76	77	110	110	112	112	110	112	110	112	112	70	72	72	72	72	68	68	72	72	98	99	99	98	99	99	99	98	99
2	Sowmya	26200	28	11	9	11.3	5	2	1	1	1	1	2	1	1	1	1	82	81	80	84	81	82	83	83	84	122	120	118	118	120	120	122	120	122	78	78	78	78	78	78	78	78	78	99	99	98	99	99	98	99	99	99
3	Mariammal	26788	47	10	8	13.3	4.6	1	1	1	2	2	1	1	1	1	1	68	69	71	73	70	69	68	67	67	136	136	134	136	138	136	136	136	138	76	78	78	78	76	76	76	76	76	99	99	98	98	99	98	99	99	99
4	Gowri	28905	42	11	9	14.3	5.8	1	1	1	1	1	1	1	1	1	1	88	86	85	84	87	88	88	87	88	102	102	104	102	102	104	102	104	104	68	68	68	68	68	68	68	68	68	98	98	98	99	99	98	99	99	98
5	Sharadha	27476	38	13	11	13.8	5.5	1	1	1	1	1	1	1	1	1	1	82	81	82	81	81	83	81	82	82	104	104	102	102	104	104	104	104	106	70	68	70	70	70	68	68	68	70	99	98	99	98	99	98	98	99	99
6	Ravi	27975	29	11	9	15.6	5.8	1	1	1	1	1	2	1	1	1	1	76	75	76	75	77	78	75	77	76	104	102	102	104	106	104	104	106	106	70	72	72	72	70	70	70	70	70	98	99	98	99	99	99	99	99	98
7	Bhaskaran	27945	50	10	8	15.2	5.8	1	1	1	1	1	1	1	1	1	1	73	71	72	74	75	74	73	71	73	134	132	134	134	134	132	134	136	136	86	88	88	88	88	88	88	84	84	99	98	99	98	99	99	98	99	99
8	Raghavan	27996	52	14	12	14.8	4.2	1	1	1	1	1	1	1	1	1	1	90	90	85	88	87	86	88	87	88	128	128	126	126	126	128	130	130	130	84	82	82	86	86	86	84	84	84	98	98	99	98	98	99	99	98	98
9	Lakshmammal	27475	46	12	10	14.7	5.3	1	1	1	2	2	2	1	1	1	1	88	86	87	90	88	89	89	86	89	126	128	126	124	124	126	128	126	128	82	84	84	84	84	84	84	84	84	99	99	98	99	99	98	98	99	98
10	Bhaskar	27556	22	10	9	11.4	5.2	2	1	1	2	2	1	1	1	1	1	76	76	74	78	79	74	75	74	78	116	116	118	118	118	118	116	116	116	78	76	76	76	76	76	76	76	76	99	98	98	99	98	99	99	98	98
11	Sachidananda	28747	24	11	10	15	4.4	1	1	1	1	1	1	1	1	1	1	76	76	75	77	78	73	76	75	77	112	114	114	114	114	112	112	110	112	72	72	74	72	74	74	72	72	72	99	99	98	99	98	99	98	99	98
12	Shivamurthy	28582	26	9	8	15.1	5.2	1	1	1	1	1	2	1	1	1	1	74	74	75	73	74	71	74	73	75	134	132	134	134	134	136	136	136	136	88	86	88	88	86	86	86	88	88	99	98	98	98	98	99	98	99	98
13	Satyaseelan	27579	17	14	13	15.7	5.5	1	1	1	1	1	1	1	1	1	1	76	84	87	85	87	86	86	88	87	132	132	134	136	136	134	134	136	136	88	86	86	88	88	88	88	88	86	99	99	98	98	98	99	99	98	99
14	Lalitha	29791	19	13	12	14.4	5.3	1	1	1	1	1	1	1	1	1	1	86	85	84	87	88	87	86	84	88	138	136	138	138	138	138	138	138	136	86	86	86	86	84	84	86	84	86	99	98	99	99	98	98	99	99	98
15	Renuka	29429	19	8	7	13.6	5.6	1	1	1	1	1	1	1	1	1	1	84	82	84	85	81	83	84	80	83	110	110	112	108	112	112	112	110	112	82	84	82	84	82	84	82	88	84	99	99	98	99	99	98	98	98	99
16	Firoz knan	27426	27	11	9	14.3	5.0	1	1	1	2	2	2	1	1	1	1	82	80	81	83	84	82	83	84	83	102	104	102	102	104	102	102	104	104	68	70	70	70	70	68	68	68	68	99	98	99	99	98	99	98	99	98
17	Mariammal	27976	37	10	9	13.6	5.9	1	1	1	1	1	1	1	1	1	1	82	80	81	84	83	83	82	84	83	106	104	108	106	106	104	108	108	108	70	68	68	68	72	72	72	72	72	99	98	99	98	99	99	99	98	99
18	Roopa	28000	33	9	8	13.4	5.1	1	1	1	1	1	1	1	1	1	1	70	71	70	71	72	72	72	71	72	112	110	112	112	112	114	114	114	112	72	72	72	72	72	72	72	72	72	99	99	99	98	99	98	99	98	98
19	Arun	28163	25	13	10	14.6	5.8	1	1	1	2	2	1	1	1	1	1	68	70	71	66	67	71	70	70	69	126	128	128	128	126	126	126	126	128	76	78	78	76	78	76	78	76	78	98	98	98	98	99	99	99	98	99
20	Devi	28421	29	11	9	13.8	4.7	1	1	1	1	1	1	1	1	1	1	68	66	66	67	68	70	70	69	69	114	116	116	116	114	114	114	114	114	74	74	76	72	72	76	76	72	72	99	98	98	99	99	98	99	99	98
21	Reshmi	29111	16	12	11	12.1	5.6	2	1	1	1	1	2	1	1	1	1	68	66	67	68	69	70	69	70	67	128	126	128	130	113	128	126	128	128	84	82	86	86	82	82	86	86	86	99	98	99	98	98	99	98	99	99
22	Prakash	29262	17	10	9	12.5	5.2	2	1	1	1	1	1	1	1	1	1	70	68	71	70	72	71	69	70	72	112	110	110	112	112	112	114	114	114	80	80	80	80	80	80	80	80	80	99	98	99	98	99	99	98	99	98
23	Balaji	29420	53	13	10	14.2	4.8	1	1	1	2	2	1	1	1	1	1	70	71	72	69	68	70	71	70	71	118	116	116	116	118	118	120	120	120	84	86	86	84	84	84	84	84	84	98	98	99	98	99	99	99	98	99
24	Bhagya	29727	32	9	8	14.3	5.0	1	1	1	1	1	1	1	1	1	1	84	84	83	82	81	84	81	83	83	108	108	110	110	110	110	110	106	110	82	88	80	80	80	80	80	80	80	99	99	98	99	99	99	98	99	98
25	Ateeq Ahmed	29999	30	12	11	12.7	5.4	2	1	1	1	1	2	1	1	1	1	86	86	84	85	84	86	88	87	88	110	110	110	112	112	112	110	112	112	72	74	70	70	74	74	74	74	74	98	98	99	99	98	99	98	99	99

26	Veerammal	30186	34	12	11	15.2	5.4	1	1	1	1	2	2	1	1	1	1	76	76	74	74	76	76	76	76	76	108	108	108	108	110	110	110	110	110	72	70	70	70	70	70	70	70	70	98	99	99	98	98	99	99	98	99
27	Gangadharal	31126	26	9	8	13.6	5.0	1	1	1	1	1	1	1	1	1	1	82	82	84	84	82	82	86	86	84	120	130	130	130	126	126	126	126	126	81	83	83	83	83	83	83	83	81	99	98	99	99	99	99	99	98	99
28	Mohan	31127	18	13	10	13.0	4.8	2	1	1	1	1	1	1	1	1	1	88	90	90	86	86	86	86	86	85	134	136	136	132	132	132	136	136	136	86	86	86	86	86	86	86	86	86	99	99	99	99	98	99	99	99	98
29	Radhika	51105	16	10	9	14.2	5.6	1	1	1	2	2	1	1	1	1	1	90	90	90	88	89	89	89	88	88	126	124	124	124	124	128	128	128	128	84	82	84	82	82	84	84	84	84	99	98	98	99	98	98	99	99	99
30	Pakkirisamy	52205	28	12	11	14.8	4.7	1	1	1	1	1	1	1	1	1	1	72	70	70	70	74	74	70	70	70	114	112	116	116	112	112	112	116	116	68	70	70	70	69	69	69	69	70	98	99	99	98	98	99	98	99	98
31	Martha	59505	46	11	9	13.8	5.2	1	1	1	1	2	2	1	1	1	1	76	78	78	78	76	76	76	78	78	122	124	124	124	120	120	120	120	120	82	82	82	82	80	80	80	80	80	98	99	99	98	99	99	98	98	99
32	Rudresh	52505	48	13	10	15.7	5.8	1	1	1	1	1	1	1	1	1	1	76	77	77	77	75	75	75	78	78	116	118	118	118	118	118	114	114	114	70	70	70	70	72	72	72	68	68	98	99	99	99	99	98	98	99	99
33	Ashokan	51205	34	9	8	14.6	5.1	1	1	1	1	1	1	1	1	1	1	74	76	75	75	75	75	75	88	75	102	100	100	100	100	100	100	104	104	68	70	70	70	70	70	70	66	68	98	98	98	99	99	99	99	98	99
34	Raman	52205	52	10	9	14.2	5.9	1	1	1	2	2	1	1	1	1	1	86	84	84	88	88	88	88	88	88	113	128	128	132	132	132	128	128	128	82	84	84	84	80	80	80	82	82	98	98	98	98	98	99	99	98	99
35	Vyshali	55005	20	11	9	11.9	5.0	2	1	1	1	1	1	1	1	1	1	84	82	82	82	82	82	82	82	82	106	104	104	106	106	106	106	106	104	70	72	72	70	70	70	71	71	71	99	99	99	98	98	99	99	99	99
36	Madanan	42267	20	11	9	15.8	5.3	1	1	1	1	2	2	1	1	1	1	82	84	84	84	83	83	84	83	83	128	126	126	126	126	128	128	128	128	82	82	82	82	82	82	82	82	82	99	98	99	99	99	98	98	99	99
37	Vairakannu	42411	30	13	10	14.3	5.6	1	1	1	1	1	1	1	1	1	1	82	80	80	80	79	83	83	83	82	113	130	130	130	130	130	130	130	130	86	86	86	84	84	84	84	84	84	99	99	98	99	98	99	99	99	99
38	Shivakumar	42299	32	14	12	13.7	5.2	1	1	1	1	1	1	1	1	1	1	70	72	68	68	68	68	68	69	70	108	110	110	110	106	106	106	106	106	68	70	70	70	70	68	68	68	68	99	98	98	99	98	99	99	99	99
39	Saraswathi	42783	38	10	9	14.1	5.5	1	1	1	1	2	2	1	1	1	1	68	70	70	66	66	66	68	68	68	122	122	122	124	124	124	124	124	124	86	84	84	84	88	88	88	86	88	99	99	98	98	98	99	99	99	99
40	Meera	45626	18	11	9	12.9	4.4	2	1	1	1	1	1	1	1	1	1	66	70	65	65	65	65	67	67	67	120	118	118	118	118	118	118	118	118	76	78	78	78	78	78	78	74	74	99	99	98	98	98	99	99	98	99
41	Muthusamy	42927	53	10	9	13.5	5.3	1	1	1	2	2	1	1	1	1	1	70	72	72	72	72	69	69	69	70	106	104	104	104	104	104	104	104	104	72	70	70	70	70	74	74	74	74	98	98	99	98	98	99	99	99	99
42	Anjalai	43001	50	13	11	12.1	5.2	2	1	1	1	1	1	1	1	1	1	86	84	84	84	84	84	88	88	87	102	104	104	100	100	100	100	100	100	70	72	72	72	72	72	72	72	72	99	99	99	99	98	99	99	99	99
43	Parameshwaran	43018	45	14	12	14.4	5.5	1	1	1	1	2	2	1	1	1	1	86	80	80	80	80	79	80	81	80	134	134	134	136	136	136	136	136	136	88	90	90	90	90	86	86	86	86	98	98	99	98	99	98	99	99	99
44	Abdul Khadir	61205	40	10	8	13.7	4.2	1	1	1	1	1	1	1	1	1	1	75	74	74	74	76	76	76	77	76	126	128	128	128	128	126	126	126	126	76	74	74	74	78	78	76	76	76	99	99	99	98	98	99	98	99	99
45	Kamal	62205	18	11	9	15.9	5.8	1	1	1	1	1	1	1	1	1	1	69	67	67	67	69	69	72	71	70	108	110	110	110	110	110	110	110	110	68	70	70	70	66	66	66	66	70	98	99	99	98	98	99	99	99	99
46	Maruthambal	62005	54	13	11	10.8	5.5	2	1	1	2	2	1	1	1	1	1	71	73	73	68	68	68	70	70	70	120	118	118	120	120	120	120	118	118	70	72	72	72	72	68	68	68	68	98	98	98	99	99	98	99	99	99
47	Saranya	61205	23	11	9	11.8	4.6	2	1	1	1	1	1	1	1	1	1	81	80	80	80	80	81	81	82	82	112	114	114	114	110	110	110	110	110	72	70	72	70	72	70	72	70	72	98	99	99	99	99	98	98	99	99
48	Seetha	44126	41	10	8	12.4	5.8	2	1	1	1	2	2	1	1	1	1	89	88	88	88	88	88	88	88	90	104	104	104	106	106	106	104	104	104	68	70	66	70	66	66	70	70	66	98	99	99	99	99	98	99	99	99
49	Krishna	43921	52	11	9	13.1	5.7	2	1	1	1	1	1	1	1	1	1	90	90	90	87	89	89	89	90	90	122	120	122	120	122	120	120	120	120	74	72	76	72	72	76	76	76	76	99	98	98	99	99	99	99	99	99
50	Moorthy	44012	44	12	10	14.5	5.0	1	1	1	1	1	1	1	1	1	1	70	72	72	72	69	69	69	70	70	110	110	112	112	112	112	112	110	110	76	78	78	74	74	74	74	74	74	99	98	98	99	99	98	99	99	99

ANNEXURE III

KEY TO MASTER CHART

Sl. No.	- Serial Number
IP No.	- In-patient number
RA	- Rescue analgesics
Yrs	- Years
Min	- Minutes
Hrs	- Hours
Post-Op	- Post-operative
PR	- Pulse rate
SBP	- Systolic blood pressure
DBP	- Diastolic blood pressure
SpO_2	- Oxygen saturation

ANNEXURE IV

List of Statistical formulae used

1) Mean : $\bar{x} = \frac{\Sigma x}{n} = \frac{\text{Sum of all the values}}{\text{Number of values}}$

2) SD = $\sqrt{\frac{\Sigma (x - \bar{x})^2}{(n-1)}}$

3) $t = \frac{\text{Difference of means}}{\text{SE of mean}}$

CONSENT FORM

I _____ hereby give consent to participate in the study conducted by **Dr.ROSHIN ANN JAMES,** Post Graduate in Anaesthesia, Department of Anesthesiology,Thanjavur Medical College and hospital,Thanjavur and to use my personal clinical data and result of investigation for the purpose of analysis and to study the nature of disease. I also give consent for further investigations

Place :

Date : Signature of Participant